The utilization of macroergonomics and simulation to improve control of healthcare acquired infections

José Mauricio Jiménez

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Brian M. Kleiner, Chair
Stephen G. Eubank
Anthony D. Slonim
Christian Wernz
John L. Robertson

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Abstract:

Background: In the United States, it is estimated that 1 in 20 patients become infected with a healthcare acquired infection (HAI). Some of the complications of HAIs include increased morbidity and mortality, and drug-resistant infections. *Clostridium difficile* has replaced methicillin-resistant *Staphylococcus aureus* (MRSA) as the most important HAI in the United States by doubling its prevalence during the last decade.

Significance of the study: This study is grounded on the subdiscipline of macroergonomics and highly detailed simulation. The Macroergonomic Analysis and Design (MEAD) model is utilized to identify and correct deficiencies in work systems. The MEAD process was applied to develop possible sociotechnical interventions that can be used against HAIs. Highly detailed simulation can evaluate infection exposure, interventions, and individual behavior change for populations in large populations. These two methods provide the healthcare system stakeholders with the ability to test interventions that would otherwise be impossible to evaluate.

Objective/Purpose: The purpose of this study is to identify the factors that reduce HAI infections in healthcare facility populations, and provide evidence-based best practices for these facilities. The central research question is: What type of interventions can help reduce *Clostridium difficile* infections?

Methods: We collected one year of patient archival information to include activities, locations and contacts through electronic patient records from two Virginia regional hospitals. Healthcare worker activities were obtained through direct observation (shadowing) at the two Virginia regional hospitals. Experiments were designed to test the different types of interventions using EpiSimdemics, a highly-resolved simulation software. A *Clostridium difficile* disease model was developed to evaluate interventions.

Results: We observed a significant drop in infection cases at a regional Hospital. There is significant evidence to link this drop in HAI infections to a sociotechnical intervention. However, there is not enough information to pinpoint the specific action that caused the drop. We additionally conducted simulation experiments with two hospital simulations. Simulated sociotechnical interventions such as hand washing, room cleaning, and isolation caused significant reductions in the infection rates.

Conclusions: The combined use of macroergonomics and simulation can be beneficial in developing and evaluating interventions against HAIs. The use of statistical control charts as an epidemiology tool can help hospitals detect outbreaks or evaluate the use of interventions. Use of systemic interventions in an *in-silico* environment can help determine cheaper, more flexible, and more effective actions against HAIs.

DEDICATION

I dedicate this dissertation to the healthcare professionals that make it their daily job to eliminate healthcare acquired infections and reduce their patients' suffering.

I also dedicate this work to my family living in multiple countries around the world. Their work in not-for-profit foundations, government, health, and the service industry is an inspiration to me.

To my grandfather Raul, who encouraged and supported my mother to study and attend college, at a time when women's education was frown upon by society. The importance that he placed on education for her, my uncles, and aunts, is one of the reasons that I can submit this work today. He was there for my graduation from West Point, but due to his illness, he will not be able to see me graduate for Virginia Tech. He is always in my heart.

Finally, I dedicate this work to my wife, Lara. You are my daily inspiration. This work is just as much yours as it is mine. I could have never been able to undertake such a project without your love, support, understanding, and patience. Thank you for twelve amazing years of love and support.

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1. Introduction

The March 2012 edition of *Vital Signs*, a publication of the Centers for Disease Control and Prevention (CDC) is dedicated to the increasing prevalence of *Clostridium difficile,* a Healthcare-acquired infection (HAI) that has increased its infection a rate by almost 400% since 2000. Although the tracking methodology for the pathogen was different in 2000 from 2007, the CDC believes that this increase is caused by a stronger bacterial strain. *Vital Signs* provided some of the basic information regarding this infectious disease and the possibility of its spread in hospital settings. Perhaps the most concerning fact about this report is that the groups at risk include immunocompromised patients, patients with long lengths of stay in a hospital, people older than 65 years, people taking certain kinds of antibiotics, and people with comorbidities (Centers for Disease Control and Prevention, 2012).

HAIs, formerly known as nosocomial infections, are a common occurrence in medical facilities around the world. In the United States, 1 in 20 hospitalized patients become infected with an HAI (Centers for Disease Control and Prevention, 2010). In 2002 alone, between 1.7 and 2 million patients acquired an HAI in the United States (Klevens et al., 2007; Research Committee of the Society of Healthcare Epidemiology of America, 2010). The World Health Organization (WHO) has estimated that almost nine percent of patients who undergo procedures in medical facilities in Europe, Eastern Mediterranean, South-East Asia, and Western Pacific acquire an HAI (World Health Organization, 2002). The ramifications of HAIs are multifaceted and very serious.

HAIs can be a source for epidemics in medical facilities due to the type of population being treated there. Many hospitalized patients are especially susceptible because they are immunocompromised, in other words their immune systems are unable to respond to infections as a healthy person's immune system would. Examples of immunocompromised patients are: the elderly, infants, children, pregnant women, cancer patients, or people with immune-mediated diseases. In addition to affecting immunocompromised patients, HAIs can affect patients that have open wounds, or are undergoing other procedures such as catheter, ventilation, or surgery (World Health Organization, 2002). It is also possible that certain medications prescribed and administered by healthcare professionals, such as commonly prescribed antibiotics, compromise the immune system. The population in a healthcare facility is a rich environment for infection spread.

Due to the over-prescription of antibiotics to patients, there now exist several "super bugs" or antibiotic-resistant bacteria such as Methicillin Resistant *Staphylococcus aureus* (MRSA), or *Pseudomonas aeruginosa*. These "superbugs" are more dangerous and harder to eliminate other infections because they have evolved through several generations to withstand antibiotics. As mentioned before, due to the type of population and the close-quarters environment of a hospital, the risk of infections by "superbugs" increases significantly. Other pathogens such as *Clostridium difficile* thrive in patients who undergo antibiotic treatment, and therefore alternative treatments must be developed to eliminate the infection (Karen & John, 2011).

The cost of preventing and managing HAIs is a significant burden on health care systems. In 2002, the cost of treating HAIs was $6.7 billion in the United States, and $1.7 billion in the United Kingdom (Graves, Halton, & Lairson, 2007). Estimates for 2009 put the average cost of managing each infection at $15,275 (Scott, 2009), although for individual patients with multi-organ sepsis the cost may be hundreds of thousands of dollars. These expenses represent a major problem for the United States, the country with the most expensive health care system (Anderson & Frogner, 2008). Furthermore, there are additional costs not counted in prior studies as healthcare expenditures such as loss of worker productivity, cost to society, and the possible loss of life. The increased demand for health care services associated with treatment of patients with infections (including prolonged stays in intensive care units), taxes, facilities, and staff make HAIs a significant burden on our society and healthcare system. In addition to the threat of infection, healthcare costs increase significantly with hospital-acquired infections due to the increased morbidity of a patient. After acquiring a secondary infection, the patient must be treated for a longer time and for more than one cause. The increase length of stay and infection control procedures creates unexpected costs for the hospital and the patient or his insurer.

HAIs affect the balance of resources in a medical facility where resources are already strained. Medical staff that would otherwise be treating other patients must now continue treating patients with secondary infections. Hospital beds that could be used for other patients continue to be occupied due to the increase in length of stay of the patient. The problem becomes a resource allocation problem for hospital administrators who must utilize their best guess on how to overcome this problem. Decisions at the management level are many times driven by financial results. The decision to better staff and equip hospitals based on hospital-acquired infections must be based on the probability of eliminating the infection or being able to obtain a return for the investment. Hospital administrators would benefit from identifying specific interventions that can be effective in controlling infections.

Clostridium difficile has become one of the most prevalent and dangerous HAI in the world. In the United States alone there are over 300,000 cases reported per year (Yoo & Lightner, 2010). *Clostridium difficile* is a normal occurring bacteria in the intestinal flora. However, certain strains such as BI/NAP1/027 can cause *Clostridium difficile*-associated disease (CDAD). CDAD can produce watery diarrhea on the mildest of cases but can also produce severe colitis requiring surgery in the harshest cases. The severe form of the infection can also lead to death. CDAD has been linked to risk factors such as age, use of antibiotics, and length of stay in a hospital (Sunenshine & McDonald, 2006). New treatments are currently being developed to fight CDAD to include new antibiotics, fecal transplants, and a new vaccine. Due to its prevalence and chain of infection C*lostridium difficile* lends itself very well for modeling and analysis.

This study differentiates itself from previous work in two different aspects. First, previous hospital simulations look at only one specific population, the patients. This ignores healthcare workers, contaminated surfaces, and hospital visitors. The simulation software utilized in this study incorporates those four populations. Secondly, interventions proposed in other studies look only at medical treatment (pharmaceutical therapy). This study investigates holistic interventions that take into account all the subsystems inside a hospital. The advantage of using simulation and macroergonomics together is that this methodology allows for more complete sociotechnical interventions that will be actionable at the hospital level.

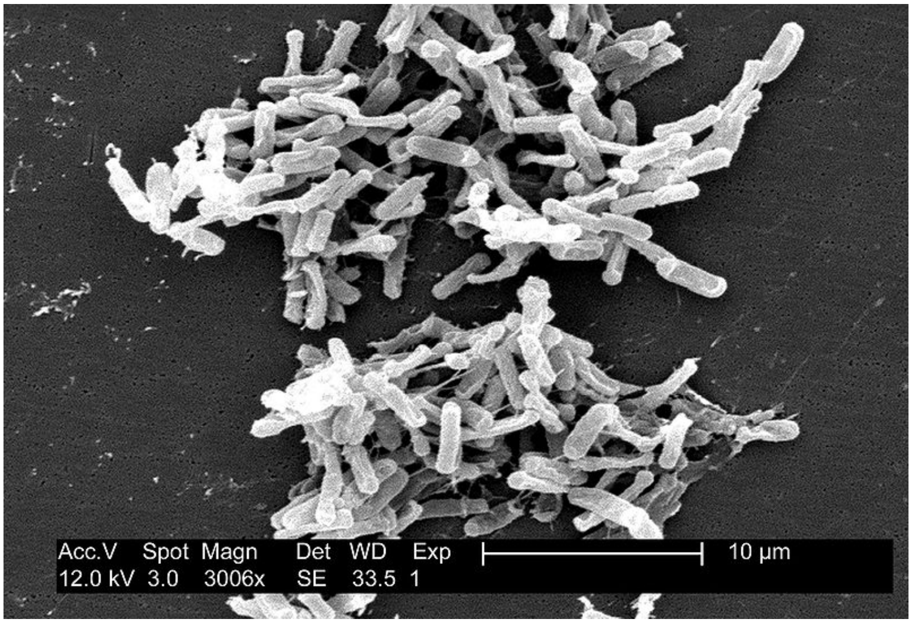


Figure 1: Scanning electron micrograph of *Clostridium difficile* bacteria from a stool sample.

(Centers for Disease Control and Prevention, 2007)

1.2 Theoretical Perspective

The philosophical worldview for this proposal is post-positivist. Postpositive worldview represents the traditional type of research approach that looks at empirical observation and measurement. The postpositive worldview is also interested in identifying what causes a specific event or outcome (Cresswell, 2009). Based on this worldview, the study will gather evidence from healthcare systems and reduce the information in a workable model based on the theory of macroergonomics.

The strategies of inquiry for this research study will be quantitative because we are interested in developing a workable model of the healthcare system by conducting detailed measurements. The research methods include data collection from the hospital staff, continuous and static observations of hospital staff, statistical analysis of the field research and patient data, construction of a system-based model of the healthcare facility (synthetic population and environment), simulation of the HAI in the synthetic environment, and evaluation of methods to determine best practices for the facility. These research methods are explained in detail in the following sections. This study will follow the framework of macroergonomics.

1.3 Purpose of the Study and Delimitations

The purpose of this study is to identify the factors that increase HAI exposure in healthcare facility populations and provide evidence-based best practices for these facilities. The central research question is: What type of interventions can help reduce or eliminate exposure to HAIs? To answer this question, this study will be grounded on macroergonomics and simulation. Macroergonomics provides the ability to develop systemic interventions in healthcare facilities and simulation allows evaluating these interventions that would otherwise be impracticable or very expensive to conduct. In order to address the main question, the study looks at the population inside two regional hospitals. This study does not analyze at factors that cause disease outside of the hospital boundaries or at interventions applied outside the hospitals. The study is limited to evaluating the dynamics inside the hospital and producing intervention suggestions that can be operationalized by the hospital staff. This study is also not concern with the operationalization of the interventions, as these are decisions that must be taken at the highest levels of the hospital administration staff. The type of interventions that the study will suggest must comply with the following criteria:

1. The interventions should follow the principles of macroergonomics.
2. The interventions should be testable using the population inside the hospitals.
3. The interventions must be testable using highly-resolved simulation.

4. *Clostridium difficile* will be used as the disease model for the study but the methodology should be generalizable to other HAIs.

The graph below shows the areas of the hospital environment that the study examines. The main concern of the study is to identify those elements that affect the transmission of HAIs, in this case *Clostridium difficile*, within the healthcare environment. The study also looks at identifying solutions as a combination of factors from within the healthcare environment.

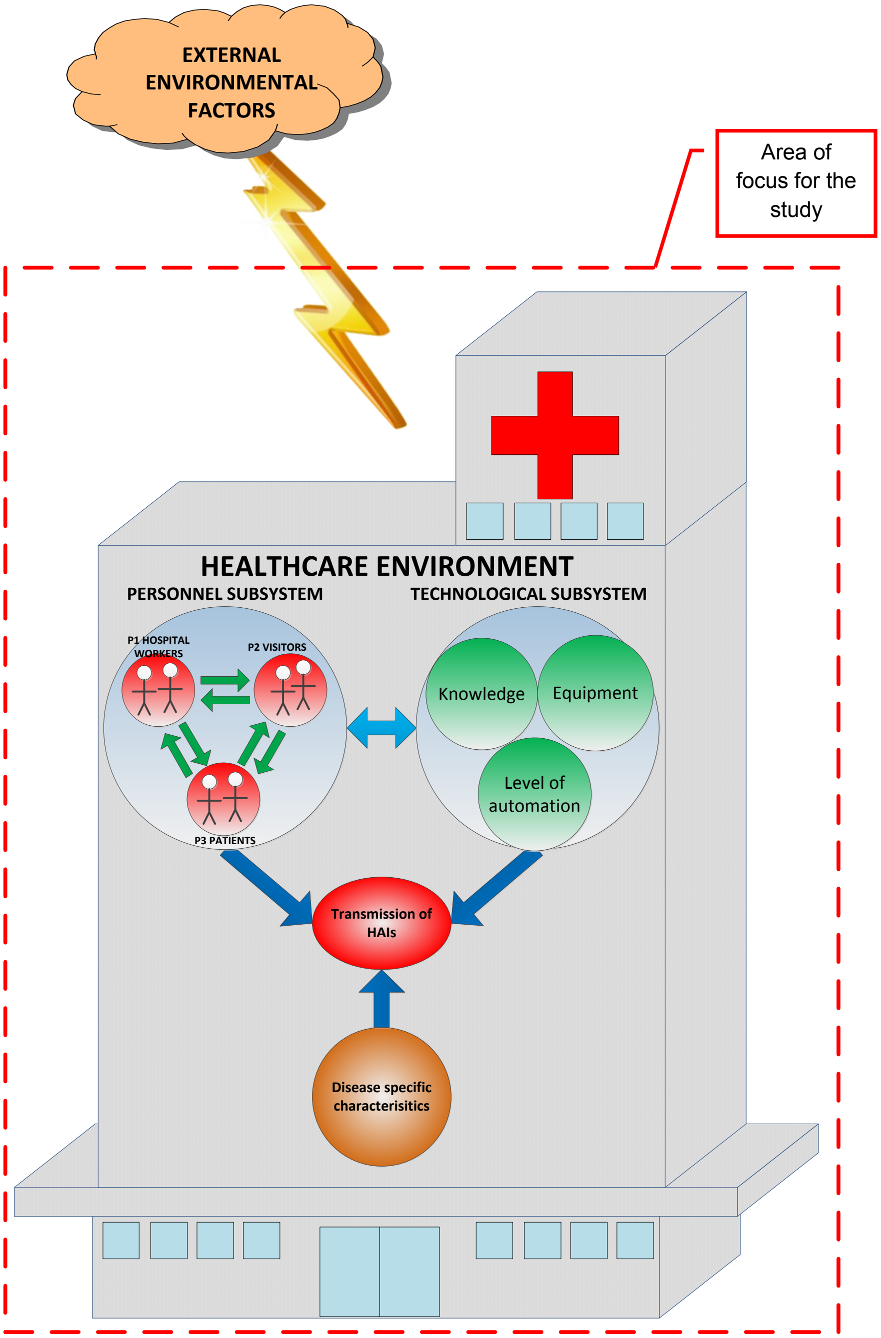


Figure 2. Study delimitations

Figure 2 above shows how the interaction of multiple subsystems within the hospital can affect the transmission of HAIs. For example, Tom, a patient (P3 subsystem) who enters a hospital for a surgical procedure is prescribed antibiotics by his physician (P1 and knowledge subsystems). The antibiotics disturb the intestinal flora in the patient, which allows *Clostridium difficile* to grow unchallenged. Later on, Tom's nurse is exposed to *Clostridium difficile* spores from another patient in the same ICU. The nurse inadvertently passes some of those spores to Tom who becomes colonized by the bacteria, and shows symptoms within 48 hours. Tom also begins to shed bacterial spores through his stool, and contaminates his room.

Another example shows the same system preventing the spread of the infection. In another scenario, Tom arrives to the hospital and he is admitted to the ICU. Another patient, John, becomes colonized with *Clostridium difficile* at a nursing home. John also arrives at the hospital, and is admitted to the ICU just like Tom. John has diarrhea, and a nurse sends a sample taken from his stool to the hospital laboratory. John is diagnosed shortly with community-acquired *Clostridium difficile.* The nurses in the ICU immediately isolate John, and begin prevention measures. The nurses also wash their hands and use protective gear to avoid contamination. These two scenarios, with different outcomes, are short descriptions of how the different subsystems interact within the internal environment of the hospital.

1.4 Research Questions

The central question for this study is:

What type of interventions can help reduce or eliminate exposure to HAIs in hospitals?

The proposed research will be directed at answering the following hypotheses:

Hypothesis 1: The exposure to *Clostridium difficile* infections can be reduced or eliminated by incorporating effective systemic interventions that center on the interaction of personnel, technology, organizational structure, and hospital environment.

Research Questions:

- Are systems-based interventions more effective in reducing the spread of *Clostridium difficile* than individual clinical treatment?
- Is there a difference in the total number of patients exposed to *Clostridium difficile* based on the number of people (patients, visitors, or healthcare professionals) that embrace specific interventions?
- Is there a specific type of intervention that centers on only one of the hospital subsystems (personnel, technology, organizational structure, and environment) that is more effective in reducing exposure to *Clostridium difficile* than other types of interventions?

Hypothesis 2: *Clostridium difficile* infections in a hospital can be effectively modeled as part of a highly-resolved computer-based simulation for the analysis of interventions.

Research Questions:

- Can simulated interventions provide an effective and efficient manner to address infection prevention and control in the hospital?
- Can simulated interventions provide better methods for cleaning and disinfection of isolated patient rooms than the ones currently in use?
- Can patient and employee safety be improved by providing solutions from simulated interventions?

Hypothesis 3: Are healthcare workers at a higher risk of acquiring *Clostridium difficile* infections in a hospital than patients?

Research Questions:

- What is the level of exposure of healthcare workers to *Clostridium difficile* infections in a hospital?

- Are there specific interventions for healthcare workers that can help reduce the exposure to *Clostridium difficile* infections in a hospital?
- Can specific interventions applied to the healthcare worker population put patients at a higher risk of acquiring *Clostridium difficile* infections in a hospital?

1.5 Preface and attribution

The manuscripts in this dissertation are organized in a manner in which they support the main research questions and objectives of the dissertation. Manuscript 1, *Reduction of Clostridium difficile rates at a regional hospital in southwest Virginia through sociotechnical interventions*, was authored by Jose M. Jimenez MPH MS MEM, Maribeth Coluni RN BSN, Bryan L. Lewis,PhD MPH, John Robertson DVM PhD, Loressa Cole DNP MBA NEA-BC FACHE, Sharron Jones RN BSN PCCN, Carrie Estes RN BSN CNOR, Lalena Pedrotti BSN MSN-ED, and Stephen Eubank PhD. Manuscript 1 addresses Hypothesis 1 by evaluating the effectiveness of systemic interventions across the hospital. A 4-stages sociotechnical intervention was utilized to reduce the *Clostridium difficile* infection rate from 8.76 to 2.23 in three years. The authors analyze the actions taken during the intervention, and utilize statistical process control charts to determine the specific point in time when the infection rates were reduced and entered process control.

Manuscript 2, *Macroergonomics and simulation: a multidisciplinary methodology to design sociotechnical interventions in hospitals,* was authored by Jose M. Jimenez MPH MS MEM, Maribeth Coluni RN BSN, Bryan L. Lewis PhD MPH, Anthony Slonim MD DrPH, Brian Kleiner PhD, and Stephen Eubank PhD. Manuscript 3, *Development of a highly-detailed, highly-resolved in-silico hospital population to simulate outbreaks of* *healthcare acquired infections*, was authored by Jose M. Jimenez MPH MS MEM, Bryan L. Lewis PhD MPH, Tina Williamson RN, MBA, Anthony Slonim MD DrPH, Thomas Kerkering MD, and Stephen Eubank PhD. Both manuscripts address Hypotheses 1, 2, and 3. These two manuscripts describe in detail the creation of the simulation model using a systems perspective. Additionally, they include multiple evaluations of systemic interventions. Finally, they address low levels of contamination of healthcare workers.

2. Literature Review

2.1 Macroergonomics

Macroergonomics is a sub-discipline within human factors and ergonomics that analyzes the relationships between individuals, technology, organizational structure, internal environment, and external environments (Hendrick & Kleiner, 2001). The more commonly known physical ergonomics looks at body measurement and physical aspects of machines. Macroergonomics takes a more systemic approach looking at how an entire process incorporates a person placing them at the center of the systems (Hendrick & Kleiner, 2001). The macroergonomics framework follows 10 specific steps: scanning analysis, system type and performance analysis, technical work process analysis, identifying variances, creating the variance matrix, creating the key variance control table and role network, function allocation and joint design, responsibility perception analysis, designing/redesigning support sub-systems and interfaces, and implementing, iterating and improving (Hendrick & Kleiner, 2001; Kleiner, 2006).

2.1.3 Macroergonomics in healthcare

There are several articles that have used macroergonomics in the healthcare realm. Karsh and Brown (2010) took the approach of reducing human errors in healthcare by addressing the organizational structure of a hospital (Karsh & Brown, 2010). The paper hypothesizes that errors in a medical facility can occur when medical professionals report to a complex organizational structure or follow complicated rules and guidelines. Nurses can have supervisors from different reporting structures. For example, a nurse can report to a nurse manager, a resident doctor, and a chief of staff all at the same time. With nested structures such as these standard operating procedures can become complex and with additional stress added to a person, errors are more prevalent. Karsh and Brown (2010) modeled a nested system using macroergonomics and mathematical equations showing multi-level structures (Karsh & Brown, 2010). The article shows a model that could help explain many of the interactions of medical personnel. Karsh & Brown (2010) show a theoretical model on evaluating complex systems; however one of the deficiencies is that it has not been tested by either simulation or implementation in a hospital.

Alper & Karsh (2009) conducted a review regarding safety violations in different industries (Alper & Karsh, 2009). They determined, by conducting a meta-analysis of 13 publications in the subject, that there is a set of factors that is associated with safety violations. These factors apply whether they are voluntary or involuntary. The article groups the factors into four categories: individual, work system, organization factors, and external environment. The interaction of those factors determines the outcome of the decision between complying with a safety guideline or violating it. Alper & Karsh (2009) provide recommendations on how to approach research on safety compliance. The article suggests utilizing the macroergonomics framework because of the interactions of the four categories mentioned above. Those four categories match the main areas within the macroergonomics framework. In addition the study recommends to use knowledge elicitation techniques such as interviews and focus groups along with quantitative techniques (Alper & Karsh, 2009).

Carayon and Wood (2010) proposed the Systems Engineering Initiative for Patient Safety (SEIPS) model. The authors propose to look at the healthcare system as a whole and not just at the infection by defining the processes and outcomes of the system

(Carayon, 2010). The model is a descriptive system that includes processes that are being performed by the separate subsystems as defined by macroergonomics. SEIPS, for example, will describe the patient care process that a person in the organization performs and the outcome such as quality of care and patient safety. Unlike in Alper & Karsh, this model is not interested in safety violations, but on the specific elements that determine an outcome (Carayon, 2010). SEIPS looks at precise elements and components of each subsystem. For example, within the person subsystem, SEIPS looks at education, skills, motivation, physical, and psychological characteristics. Carayon & Wood suggest specific interventions with their model in order to understand a healthcare system. Some of these interventions were used for an outpatient surgery facility and they include: staff surveys, shadowing of patients, review of floor plans, employee questionnaire, and patient surveys (Carayon, 2010).

Macroergonomics is a very useful framework to establish the subsystems of a larger system, aid in characterization and reduction but it shows several gaps in practice. Macroergonomics is mostly a descriptive method; it allows the researcher to develop a simplified but accurate view of a facility, in this case a healthcare facility. Although some models have tried to develop mathematical relationships between the subsystems, it is challenging to verify them or to put into practice the recommendations that these models provide. One way to use the macroergonomics-based model and test interventions is through simulation. Simulation allows a researcher to construct a representation of a facility and experiment with different interventions in a safe and cheap manner. There is a tremendous opportunity in combining macroergonomics and highly-resolved simulation.

2.2 Highly-resolved simulation of infectious diseases

Simulation has been used before to help explain the complexities of healthcare system. There are different types of simulations and each has specific advantages and limitations. Simulations are representations of complex systems and they can never be a perfect representation of reality. Additionally, one cannot say that any simulation is better than the other. Some simulations may be better suited for a specific scenario compared to others. Keeling and Rohani (2008) present a spectrum of computer simulations based on the proximity to the ability to represent the conceptual model in a more graphical (user-friendly) manner, or represent the model directly in computer code. Examples of more graphical types of simulations include WEAP, Glumso, and the popular game SimCity. These types of simulation are very user-friendly and easy to learn. Systems Dynamics simulations or ordinary differential equation (ODE) models such as VenSim and PowerSim are located close to the middle of the spectrum. These simulations also present a graphical interface for the conceptual model, but provide the ability to code equations and interactions between health states. These simulations aggregate information by using differential equations. The most computer code-intensive simulations include simulations written directly in C, C++, or Java language. This last type of simulations can provide better resolution but require training and users that are computer-code savy (Keeling & Rohani, 2008).

2.2.1 Mathematical Models

Perhaps the most important model regarding infectious disease simulation is the original Susceptible-Infected-Removed (or Recovered) (SIR) model by Kermack and McKendrick (1927) (Kermack & McKendrick, 1991). This model helped epidemiologist first understand the importance of patient movement from one health state to another through the use of differential equations. The SIR model has been improved significantly since it was first published, but in one way or another most of the models continue to use some of the original ideas behind SIR. A popular type of mathematical modeling is a compartmentalized model. These types of models have a fixed patient population that moves from one health state to another following some type of statistical distribution or incorporates stochasticity. Starr and Campbell propose a reversible jump Markov Chain Monte Carlo model. They claim that traditional models may not be applicable or are inappropriate to simulate small outbreaks of infections such as *Clostridium difficile* because those models tend to aggregate for larger patient populations. This Markov model uses Bayesian statistics to account for missing information, and hidden states. The model uses three reservoirs of the infection in a hospital, the environment, patients with *Clostridium difficile* and toxins, patients only with toxins, but does not account for other groups of people in the hospital (Starr & Campbell, 2001). A newer model by the same authors uses a spatio-temporal compartmentalized model. This new model includes health states for patients described as immune, susceptible-uncolonized, susceptible-colonized, toxin positive and utilizes an exponential distribution to move patients from one state to another (Starr, Campbell, Renshaw, Poxton, & Gibson, 2009). Lanzas et al. (2011) also use a compartmentalized model with health states defined as resistant, susceptible, asymptomatic colonization with negative *Clostridium difficile* infection, asymptomatic colonization with positive *Clostridium difficile* infection, and diseased. The models use hospital information from patients as parameters including a basic reproduction number (R_0) of 0.55 to 1.99 with a median of 1.04 (Lanzas, Dubberke, Lu, Reske, & Grohn, 2011).

2.2.2 Decision Tree Models

Some researchers have combined the ease of use of decision trees with the power of Monte Carlo simulation (McGlone et al., 2011). Lee et al. (2010) proposes two models to determine the value of creating and using a new *Clostridium difficile* vaccine with a synthetic population cohort of 5,000 patients. The two models are depicted using Treeage Pro 2009, a decision tree modeling software that can be combined with simulation tools. One of the models depicts the decision of whether or not to administer *Clostridium difficile* vaccine to patients at risk, while the second model depicts the decision of whether or not to administer the vaccine to prevent recurrence of CDAD. The basic initial prevention model starts with the decision to vaccinate or not, then moves into a probability node that decides whether a patient colonized or not. The next node splits into whether the patient has become infected (toxins are present); the last probability node describes whether the infection is severe or mild. The second decision model looks first at whether the initial treatment is effective or ineffective treatment and therefore there is a relapse of CDAD. The tree then splits into more iterations of the first model. This particular model measures the effectiveness of the vaccine in Disability-adjusted life years (DALY) a universal measurement that can looks at the Years of Life Lost (YLL) and the Years Lived with Disability (YLD) due to the effect of a specific disease. Sensitivity analyses were then performed with different costs for the vaccine. The model provides evidence that the use of a vaccine would be economically efficient over most of the scenarios (Lee, Popovich, et al., 2010).

2.2.3 Systems Dynamics Models

System dynamics have several advantages that make them attractive to researchers and epidemiologists due to their graphical user interface (GUI) and the power of differential equations. Some of the advantages include the ease of learning the software. A person with no prior experience in simulation can learn to develop scenarios in a few hours. Additionally, there are several commercial software programs (such as VenSim, PowerSim, STELLA or AnyLogic) that can be quickly downloaded from the Internet and that provide enough functions to create detailed models. VenSim for example has a capability to develop charts on stock variables and slide-bars on rates to adjust them for sensitivity analysis. Software like VenSim can be utilized to describe complex systems by drawing causal loop or stock and flow diagrams. This drawing feature makes the process of creating a simulation less code intensive. VenSim can also create visual "Flight Simulators" or control dashboards of the variables in a model. These variables can be changed the same way that one dials a radio and the results of the simulation are observed instantly (Sterman, 2000; Ventana Systems, 2011). Although System Dynamic models are easy to learn, user-friendly, and visually pleasing compared to more code-oriented simulation models they are abstract in nature and do not provide a high level of resolution. For example, a Systems Dynamics model would show the relationships between health states in an infection model but it aggregates the population so that it is impossible to differentiate between any individual people being infected. Agent-based modeling and highly-resolved simulation overcome this downside.

2.2.4 Agent-Based Modeling

Agent-based modeling (ABM) is another type of simulation that looks at deeper granularity and resolution. Schelling (1971 and 1978) proposed a model to look at segregation over time for cities in the United States. He proposed an initial model with two types of agents (red and green) uniformly spread in a field of spaces with some empty spaces. The agents have simple instructions that make them look for empty spaces that are close to other agents of the same color. Over time the agents start clustering by color (Schelling, 1971, 1978). The Schelling model is one of the most basic but groundbreaking examples of ABM. Newer ABM simulations have been developed for uses in the healthcare arena. Some of these models look at the implementation of policies to reduce HAIs. Laskowski & Mukhi (2009) propose a Linux/C++based agent simulation of an HAI flu-like infection in an emergency department. The model incorporates a graphic user interface (GUI) represented as a two dimensional representation of the emergency room with Cartesian coordinates. The representation shows the conceptual flow of the patients through the emergency department floor. The model looks only at patients (Laskowski & Mukhi, 2009). Some of the advantages of ABM simulations are the ability to use individual agents with their own behavior to interact in a more realistic environment. Some of these models can utilize realistic data as input such as national census data or the National Health Interview Survey (Lee, Brown, et al., 2010) and present solutions that are usable by government or private institutions. ABM simulation also allows the researcher to conduct realistic experiments (Kanagarajah, Lindsay, Miller, & Parker, 2010) for scenarios that would be impractical or economically restrictive to conduct in the “real” world. Other models such as Systems Dynamics or compartmentalized designs may be inflexible for patients' individual attributes and for spatial considerations (Meng, Davies, Hardy, & Hawkey, 2010).

2.2.5 Network models and Synthetic populations

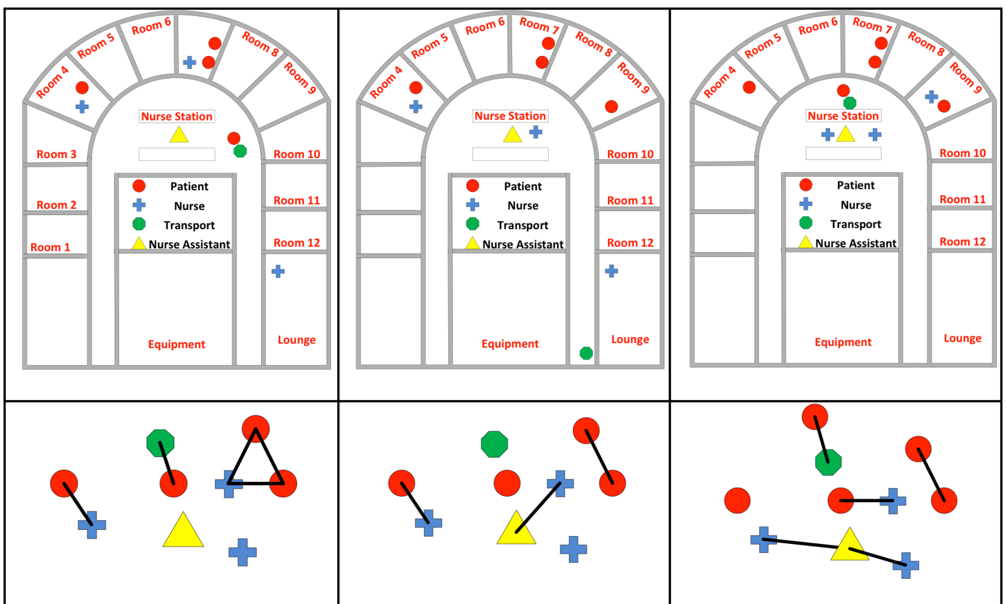
Social Network Theory (SNT) has been used in settings such as communications, politics, and healthcare. SNT origins lay in the field of sociology and the study of interactions between people. A social network occurs when a person (or node in a diagram) comes into contact with another person. This is similar to role networks in macroergonomics. This contact can be represented as a line connecting the two nodes or an edge. When multiple people come in contact then the connections become more complex, and these connections can be represented in a social network diagram or sociogram. Some of the important parameters of SNT include the people in the network, the frequency of the interactions between people, the types of interactions. Relationships in the network can be characterized by how individuals interact with each other (centrality), if the relationships between individuals are one or two-way (reciprocity), the clustering of groups or cliques, and the communication patterns in the network (Edberg, 2007).

An evolution in SNT is the ability to incorporate computational methods for analysis of large networks. One of the critiques of SNT is the inability to be used for large networks due to its complexity and difficulty in evaluation. A way to compensate for that limitation is using high-performance computing. Another limitation is the ability to collect information of very large populations due to time and resource constraints. One way to overcome this limitation is by utilizing available population information such as the national census to build computer-based or *in-silico* populations. *In-silico* populations are representations of a real population that an aggregate level they are identical to the real population, but at the individual level they are very different (Lewis, 2011). An example of synthetic simulations is Beckman et al (1996) representation of a synthetic population for transportation. This model used data from the 1990 national census to create a methodology for individual travelers in the United States. The model made selections of household for the synthetic population and then validated the synthetic population by comparing demographic characteristics of synthetic populations with true population with variables not involved in generation of simulation (Beckman, Baggerly, & McKay, 1996).

First principles have been described in order to develop successful large network synthetic population simulations. Barrett et al. (2009) describe a methodology for building complex social networks. Modeling of this level has been used to simulate every individual in the United States with activities, locations and contacts. The first step in developing the simulation is the creation of a synthetic population or proto-population. In other models that describe epidemics or pandemics in large areas, the use of massive databases was needed to replicate the population of a city (Eubank et al., 2004), a region, or an entire country (C. Barrett et al., 2009; Chao, Halloran, Obenchain, & Longini, 2010). The second step is the development of the dynamic social contact network. This encompasses creating activity templates that determine the location, activity, and duration of the activity of every member of the population. People can then have contact with another person if they happen to be together at the same location and at the same time. In the case of an infectious disease simulation, the third step involves developing the disease model that will be used to "infect" the proto-population. Information gathered from the literature serves as the basis to build the disease model as a probabilistic finite-state machine (FSM), a state-transition model that will be used on the entire proto-population. Infection parameters in the form of probabilities and distributions can then be fed into the FSM in order to develop a realistic model of how the disease will spread inside the hospital (C. Barrett et al., 2009).

EpiSimdemics is a novel simulation software that looks at synthetic simulation in large social networks. EpiSimdemics is a parallel scalable algorithm used to simulate the spread of infectious diseases over extremely large contact networks. This algorithm can also simulate other population factors such as fear and behaviors. The Network Dynamics and Simulation Science Laboratory (NDSSL) at Virginia Tech developed EpiSimdemics, with the objective of studying the effects of pharmaceutical and non-pharmaceutical interventions. EpiSimdemics is based on SNT, but can overcome its limitations of use for only small groups of people. Prior studies have used this tool for analysis of large populations at a scale of 100,000,000 people. In the simulation people and locations are identified as nodes in a network graph (sociogram) and the edges between the nodes are considered visits of a person to a specific location. The visits are specified through a schedule that includes the person, the location, the activity, and the duration of the activity. Interactions between people are calculated using a stochastic model. If one or more individuals are in the same location as an infected individual then they might or might not become infected based on probability calculations. Other simulation models do not have the same level of resolution that EpiSimdemics has due to the ability to utilize extremely large populations through social networks. Other advantages of EpiSimdemics are the ability to combine policy interventions as well as individual behaviors in the same model. NDSSL has used EpiSimdemics for several studies of large populations for multiple government agencies (C. L. Barrett, Bisset, Eubank, Feng, & Marathe, 2008; Keith R. Bisset et al., 2012; Keith R. Bisset, Feng, Marathe, & Yardi, 2009).

EpiSimdemics has the distinct ability to quantify not only the number of people that become infected with a specific disease but it can also identify the contacts between individual agents in the simulation. These contacts occur for different times depending on the activity and location of the person-agent. The software can count the number of contacts and the time that each contact lasts. Figure 3 below, shows an example representation of contacts in an ICU's social network. Every time that there is an agent-to-agent contact the software can keep a record of its location, time, and interactions.



1. Contacts between nurses and patients, patient and patient in the same room, and transportation and patient.	2. Contacts between nurse and patient, nurse and nurse assistant, and patients in the same room.	3. Contacts between two nurses and nurse assistant, transportation services and patient, nurse and patient, and two patients in the same room.

Figure 3. Contacts at different times in an ICU social network.
The red circles represent patients, the blue crosses represent nurses, the green hexagons represent transportation services, and the yellow triangle represents the nurse assistant.

2.3 *Clostridium difficile* infections

2.3.1 Microbiology

Clostridium difficile is an obligate anaerobic, gram positive, spore forming rod bacteria that is part of the normal intestinal flora in every person (Karen & John, 2011). The normal intestinal flora is a barrier against many pathogens, however when antibiotics disturb the flora, it becomes susceptible to overgrowth of bacteria such as *Clostridium difficile*. *Clostridium difficile* was initially isolated in the stools of healthy newborns in 1935 by Hall & O'Toole and identified as *Bacillus difficile* (Hall & O'Toole, 1935). *Clostridium difficile* can travel by spore and it can remain in external environments for months. CDAD is produced not by the bacteria but by the two toxins that it produces, toxins A and B. These toxins affect the intestine by creating a pseudo membrane that can cause colitis. The toxins do not affect certain demographics, for example, infants are refractory to the toxins even though this population can be colonized 5% to 70%. It is believed that this immunity maybe caused by Colostrum or because infants lack receptors for the two toxins (Lyerly, Krivan, & Wilkins, 1988; Sunenshine & McDonald, 2006).

The most common strain of *Clostridium difficile* is a new hyper virulent strain designated B1, NAP1, ribotype 027 toxinotype III. This strain is highly resistant to fluoroquinolones, and it produces 16 times more toxin A, and 23 times more toxin B. The reason for this increase in toxin is a partial deletion of tcdC gene, which regulates toxin production (McDonald et al., 2005; Yoo & Lightner, 2010). In a study of 187 *Clostridium difficile* isolates from 8 healthcare facilities in 6 states the new strain accounted for over 50% of the isolates from all the healthcare centers. The virulence of this strain is significant higher than historic strains to include higher resistance to the most popular types of antibiotics (McDonald et al., 2005).

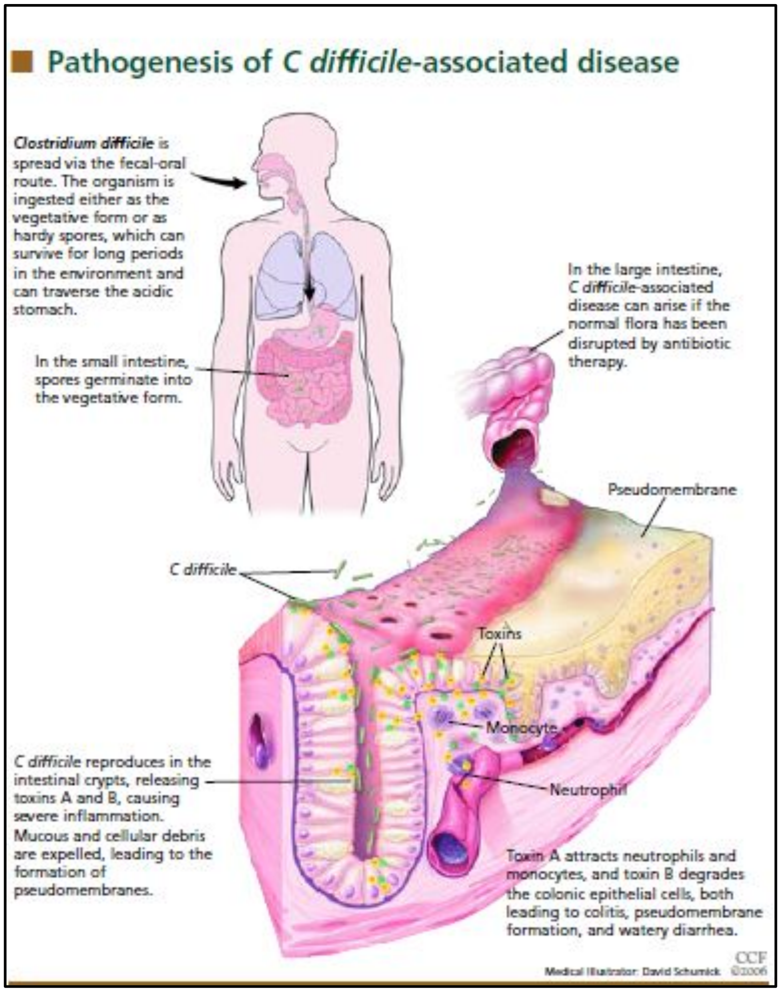


Figure 4. Pathogenesis of *Clostridium difficile* (Sunenshine & McDonald, 2006).

2.3.2 Case Definition of Clostridium difficile

Clostridium difficile was not perceived as a pathogen until the 1970s, when it was determined that there was a relationship between *Clostridium difficile* and pseudo membranous colitis (PMC). The disease was first designated as "clindamycin colitis" because of the link between patients taking the antibiotic clindamycin and the onset of PMC. Later it was determined that other antibiotics can cause the infection (Lyerly et al., 1988).

In order to understand CDAD data from healthcare facilities, it is important to understand the approved definition used in the United States by the Centers for Disease Control and Prevention (CDC). A panel of experts known as the "Ad Hoc *Clostridium difficile* surveillance working group," has decided by consensus the criteria for diagnosis of CDAD. These criteria are used officially in the United States but are also used by other countries. CDAD in a patient is confirmed if the patient follows one or more of the approved criteria:

1. A positive result in a laboratory assay for toxins A or B
2. Pseudomembranous colitis (PMC) observed during endoscopy or surgery
3. PMC observed during a histopathology examination

In addition to diagnostic of CDAD a case of recurrent CDAD can be diagnosed if the new episode occurs eight weeks or less from the previous episode.

A case of severe CDAD is diagnosed if the patient meets any of these criteria 30 days after the onset of CDAD:

1. Admission to an Intensive Care Unit due to CDAD
2. Surgery due to toxic megacolon, perforation, or refractory colitis
3. Death caused by CDAD within 30 days after onset

Furthermore, the official definition of *Clostridium difficile* and CDAD hospital epidemiologists use several classifications to identify the source of the infections. These classifications are:

1. Healthcare facility onset, healthcare facility-associated (HFO-HFA): patient with CDAD onset more than 48 hours after admission
2. Community onset, healthcare facility associated (CO-HFA): onset less than 48 hours after admission, and less than 4 weeks since the last discharge
3. Community associated (CA): CDAD symptom onset in the community or less than 48 hours since admission, and 12 weeks after being discharged last
4. Intermediate disease: case that does not fit any of the above criteria for setting
5. Unknown disease: exposure cannot be determined

The rate for C. diff cases is officially calculated as: [number of case patients per reporting period/number of impatient days per reporting period] * 10,000 = rate per 10,000 inpatient days (McDonald et al., 2007).

2.3.3 Epidemiology of Clostridium difficile

The normal presentation of CDAD includes a range of symptoms. Mild disease includes mild non-bloody watery diarrhea and low abdominal cramps. Severe presentation includes PMC and patients can develop toxic megacolon. The severe infection can lead to sepsis or death. Transmission of CDAD occurs via oral-fecal route following contamination of hands of patients and healthcare workers or contamination of the environment (patient room or fomites). There have also been reports of infection acquisition through a zoonotic route (domestic animals contaminating their owners, or through the contamination of food (Gould & Limbago, 2010; Rodriguez-Palacios et al., 2009). However the zoonotic or food borne contamination routes are far less likely to cause infections compared to the colonization of immunocompromised patients. CDAD is also the causative agent of PMC with 95% of patients with PMC being attributed to

CDAD. CDAD is also the major cause of hospital antibiotic-associated diarrhea (AAD) with 15% to 25% of patients with AAD being attributed to CDAD (Bagdasarian & Malani, 2010; Karen & John, 2011; Sunenshine & McDonald, 2006). Relapse of CDAD occurs in 10-25% of cases, making treatment long and costly. It is believed that only one third of colonized patients develop symptoms, and two thirds may develop appropriate IgG antibodies directed at the toxin (Yoo & Lightner, 2010).

CDAD has been on the rise since the 1980s and continues to increase in prevalence more than likely due to the new hyper virulent strain B1, NAP1, ribotype 027 toxinotype III. From 1987 to 1998 the mean rate of CDAD was 12.2 cases per 10,000 inpatient days (Sunenshine & McDonald, 2006). The mortality rates from CDAD increased from 5.7 per million in 1999 to 23.7 per million in 2004. CDAD was also the cause of death for 20,642 persons between 1999 and 2004. Statistics for demographics of all the patients affected with CDAD are as follows: 90% were white or Caucasian, 6% African American, 3% Hispanic, 1% Asian/Pacific Islander, and less than 1% American Indian/Alaska Native. The largest age group affected by CDAD were 75 to 84 year-old patients with 38% of the population, followed by people over 85 years-old with 37%, and 65 to 74 year-old patients with 16% (Redelings, Sorvillo, & Mascola, 2007). A study of 18,050 hospitalized patients revealed that out of 390 confirmed *Clostridium difficile* cases, 51% were over 65 years-old, making it the largest demographic (Dubberke, Butler, et al., 2008). *Clostridium difficile* is not associated with any specific ethnicity as it mirrors the nearby break down of the population. *Clostridium difficile* infection is also not associated with any particular region in the United States and it has been found in hospitals in every state (Dubberke et al., 2010). Review of data by several studies confirms that CDAD has increased at a rate of 35% per year in CDAD-associated deaths and 23% per year in hospitalizations (Zilberberg, Shorr, & Kollef, 2008). CDAD has been especially prevalent in hospitals and nursing homes. It is estimated that between 0.6 to 1.5% of patients who have contracted CDAD at hospitals or nursing homes die from the disease. Prevalence of *Clostridium difficile* colonization in long term care facilities is 4% to 20%; however colonization is less than 3% in healthy adults which means that the infection has a specific association with those who are immunocompromised (Sunenshine & McDonald, 2006). Every year the Healthcare Cost and Utilization Project (HCUP) collects information on disease and mortality causes. The latest information regarding *Clostridium difficile* is from 2009. In 2009 there were 336,600 hospitalizations due to CDAD. This number represents 0.9% of all the hospital stays in the United States (Lucado, Gould, & Elixhauser, 2012).

Clostridium difficile has been associated with very specific risk factors, among them age and use of antibiotics. Of all of the healthcare-acquired CDAD infections reported, 90% occurred during or during antimicrobial therapy, almost all antimicrobial agents have been associated with CDAD, specifically fluoroquinolones (Bagdasarian & Malani, 2010; Karen & John, 2011; Sunenshine & McDonald, 2006; Yoo & Lightner, 2010). In addition to antibiotics, age plays a very important role in the onset of *Clostridium difficile*. The average age for primary or secondary infection in patients with *Clostridium difficile* is 67.9 years-old. The age of all other patients is 48.1 years-old (Lucado et al., 2012). The following risk factors have been regularly associated with *Clostridium difficile* infection and CDAD.

a. Being 65 years-old or older

b. Suffering a severe underlying illness
c. Going through a nasogastric intubation
d. Taking antiulcer medications
e. Having a long hospital stay

(Bignardi, 1998; Sunenshine & McDonald, 2006)

A recent study suggests that there is a significant rise in the incidence of *Clostridium difficile* infection in children. A review of all discharges from the Kids' Inpatient Database from HCUP revealed that the incidence rate of pediatric CDAD-related hospitalizations increased from 7.24 cases per 10,000 inpatient days to 12.8 cases per 10,000 inpatient days from 1997 to 2006. This represents a 9.0% increase annually. The lowest infections rates were for newborns at 0.5 cases per 10,000 inpatient days. However, the age category of 1 to 4 years-old had an incidence rate of 44.87 cases per 10,000 inpatient days. The authors of the report suggest that this increase might be related to a novel strain (Zilberberg, Tillotson, & McDonald, 2010).

2.3.4 Infection Control

Infection control and prevention in the hospital is of the outmost importance when facing *Clostridium difficile* infections. There are several institutions that have published guidelines for infection control regarding this organism to include the World Health Organization (WHO), the CDC, the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Association for Professionals in Infection Control and Epidemiology (APIC). The two common reservoirs for *Clostridium difficile* infection in a hospital are colonized patients and inanimate objects. The chain of transmission includes several routes. One of the most common is using medical devices on a colonized patient and then using the same medical device on a susceptible patient. Another common route of transmission is through the hands of a healthcare worker who has been in contact with a colonized patient. Finally, there could be a route of transmission from the colonized patient to the healthcare worker, to a fomite ending in contact with a susceptible patient (Carrico, 2009). One of the most common recommendations and probably the most useful is compliance with hand washing with soap and water for healthcare professionals, patients, and visitors to a hospital. Alcohol-based gels or dispensed liquid does not kill the *Clostridium difficile* spore. In addition to hand washing, CDAD patients are to remain isolated from the rest of the hospital population. This recommendation implies that only the necessary personnel should enter the room at any time. Additionally, any person entering an isolated room should latex gloves and protective gowns to avoid spread of spores through their clothes or lab coats. These contact precautions are extremely important when the patient is having diarrhea, and should follow a minimum of 48 hours after the patient has had diarrhea (Carrico, 2009; McDonald, 2005; Rutala & Weber, 2010; World Health Organization, 2002).

Environmental cleaning and disinfection of rooms is another very important component of infection control for *Clostridium difficile*. *Clostridium difficile* spores have been found on hospital patient rooms up to five months after the infection (Bagdasarian & Malani, 2010). For this reason it is important to properly identify those rooms with *Clostridium difficile* patients even after they have vacated the room. Furthermore, all surfaces with the potential to harbor spores must be decontaminated room and environmental sources such as bed linen, patient gowns, latex gloves, healthcare professional gowns or other soft material that has come in contact with the patient must be removed, destroyed or sanitized. Any hospital equipment that comes in contact with the patient should also be sanitized and disinfected. The best type of sanitizing agent against *Clostridium difficile* spores is sodium hypochlorite (bleach) containing cleaning agents (Cohen et al., 2010; Rutala & Weber, 2010).

In addition to hand hygiene and environmental cleaning there are other recommendations regarding precaution interventions. One of the most important support systems that the patient can have during a hospitalization is his or her family. Unfortunately, a patient's family is not necessarily trained in infection control. Educating the family of the patient about the risks of CDAD should be a priority for the healthcare staff. Moreover, members of the environmental cleaning staff, healthcare administrators, and any member of the hospital staff should undergo education on epidemiology and transmission of CDAD (Peterson & Robicsek, 2009). All the institutions dedicated to the control and prevention of infectious diseases have made it clear that *Clostridium difficile* infections can only be prevented with a combination of hygiene stewardship and clinical treatment.

2.3.5 Policy development

One of the most important aspects of infection control for *Clostridium difficile* or any other HAI is policy development. Any organization in order to follow their mission must provide clear regulations and policy control. A hospital cannot be the exception especially due to the sensitive nature of the work they perform. Both hospitals observed during the pilot study have specific processes on how to create and modify procedures. Hospital 1 has a central infection control committee integrated by the Chief of Infection

Control and the heads of every department in the hospital. Every policy must be approved and signed by the committee before it is disseminated to the hospital. Every department is free to determine their own policies as long as they add levels of safety to the infection control procedures (Sturgill, 2012; Williamson, 2012). Hospital 2 does not have an infection control department but the patient safety and quality committee review and approve changes in the infection control policies as needed (Coluni, 2012).

2.3.6 Treatment

Once a patient has been positively diagnosed with a *Clostridium difficile* infection, there are several clinical treatments that can be used to help fight the pathogen. The use of any of the clinical treatments depends on the severity of the disease. The most common treatment for mild disease is oral or rectal antibiotics such as Metronidazole, Vancomycin, or Bacitracin (Tomkins, Raynor, Rothwell, DeSilva, & Wilson, 2011; Yoo & Lightner, 2010). It is not recommended to treat colonized but asymptomatic patients. For patients who are having a relapse, it is recommended to administer pulsed Vancomycin, oral or rectal administration every 3 days. Vancomycin is also recommended for severe cases of CDAD (Yoo & Lightner, 2010). In a study of 189 patients, 97 patients responded to initial antibiotic therapy, and another 78 patients responded to specific Metronidazole. The physician should allow treatment to take effect in 6 to 7 days of therapy (Sunenshine & McDonald, 2006).

Severe CDAD can produce toxic megacolon in certain patients. This type of condition is extremely lethal and must be treated immediately. In addition to treatment with antibiotics a severe infection of this type might require a colectomy, the partial or total removal of the colon (Bagdasarian & Malani, 2010; Bobo, Dubberke, & Kollef, 2011; McDonald et al., 2007). This procedure is extremely dangerous, very costly and is performed only for infections that can be lethal.

In recent years there has been development of alternative treatments that may prove to be cheaper and more effective than the standard treatment. The first example of alternative treatment is Fecal Microbiota Transplantation (FMT). FMT is not a new procedure but has not been utilized much due to the availability of antibiotics. FMT has shown great promise due to its effectiveness and the inexpensive nature of the protocol. FMT consists in the collection of a stool sample from a person with healthy and normal intestinal flora. The stool sample is filtered and combined with saline solution or other liquid. The solution is then introduced into the patient during a colonoscopy, or through a nasal-gastrointestinal tube. The procedure is not pleasing, but has been performed successfully for many years. Similar procedures called transfaunations are performed in animals. Literature review shows an effectiveness of 89% (Brandt & Reddy, 2011; Lyerly et al., 1988; Yoo & Lightner, 2010). A study was performed on 26 patients with relapsing *Clostridium difficile.* All 26 patients underwent FMT through colonoscopy. The FMT was 92% effective in preventing diarrhea or *Clostridium difficile* relapse. FMT donors for this particular study included close family members (Kelly, de Leon, & Jasutkar, 2012). Another type of alternative treatment includes the use of probiotics. A meta-analysis of all available treatments including probiotics shows a risk reduction of 44% for antibiotic-associated diarrhea and 71% for CDAD. However, there is a chance of publication bias due to the lack of published material on this (Avadhani & Miley, 2011).

The development of a vaccine against *Clostridium difficile* infection has been studied for some time. The science behind the vaccine is to increase the antibody response to the two toxins released by the bacteria (Oberli et al., 2011). Immunity has been achieved in animal models of the vaccine (Kyne & Kelly, 1998). The vaccine was also successfully tested on healthy volunteers producing an increase in the antibody response (up to 50 times higher) against the toxin A (Aboudola et al., 2003). Another type of vaccine, a synthetic DNA vaccine, has been tested in animal models (mice) proven to be significantly effective against toxin A (Gardiner, Rosenberg, Zaharatos, Franco, & Ho, 2009).

Another way to control a possible outbreak of *Clostridium difficile* infection is through the use of a "bundle." A bundle is an example of holistic or systemic interventions on HAIs. Bundles include not only clinical treatment of the disease, but the implementation of guidelines, education, patient care, infection surveillance, and active control. The use of bundles has proven to be very successful in the treatment of HAIs. Miller et al. (2010) describes the use of a bundle for the treatment of HAIs that included clinical treatment, hand hygiene, environmental cleaning, and an electronic dashboard to monitor patients at risk. This particular intervention was successful in reducing ventilator-associated pneumonia (VAP) events by 25%, catheter-associated urinary tract infections (CAUTIs) by 76%, and central line-associated bloodstream infections (CLABSIs) by 74% from 2006 to 2008 (Miller et al., 2010). Another example of systemic interventions occurred in a Scottish hospital during an outbreak of a strain of high-level clyndamicin-resistant ribotype 106 *Clostridium difficile*. The outbreak included 9 cases in a 26-room ward. The infection was controlled through the combination of deep cleaning and disinfection, closure of the ward, enforcement of isolation precautions, the implementation of an education program, open communication, and a regiment of antibiotics (Ratnayake et al., 2011).

2.3.7 Costs

In addition to the repercussions of *Clostridium difficile* infection for the patients, the costs for the treatment of the infection are enormous. A recent review of HCUP data revealed that the mean cost of all CDAD treatment for any patient could be as high as $24,400 and the aggregate costs of all CDAD treatments in the United States was $8,238,458,700 in 2009. Of the total $8 billion in CDAD costs 67.9 percent was covered by Medicare, 9.1 percent by Medicaid, 18.8 percent was covered by private insurance (Lucado et al., 2012). Several studies have estimated the cost of treatment between $3,000 and $32,000 (Dubberke, Reske, Olsen, McDonald, & Fraser, 2008; Dubberke & Wertheimer, 2009; Kyne, Hamel, Polavaram, & Kelly, 2002; Scott, 2009). However, the cost of the treatment varies due to the study approach, the length of stay of the patient, and the sample size. Additionally, the cost of CDAD treatment has increased through the years and some of the publications include data from the 1990s that is most likely not updated.

3. Manuscript 1: *Reduction of Clostridium difficile rates at a regional hospital in southwest Virginia through sociotechnical interventions*

Abstract

Background: During the last decade, *Clostridium difficile* infections has more than doubled in the United States. Treatments include antibiotics such as metronidazole, vancomycin, and fidaxomicin, and recently, fecal transplant. Known preventive measures include patient isolation, hand hygiene, and personal protective equipment.

Methods: In 2010, a 146-bed regional hospital began a campaign to reduce *Clostridium difficile* infections. The intervention included assessment of current knowledge on prevention practices, hands-on education, and monitoring of prevention practices. Medical therapy and prevention measures were not interrupted or changed during this campaign. We retrospectively analyzed *Clostridium difficile* case data for the hospital from 2009 to 2013. We utilized statistical process control to analyze the effectiveness of the intervention.

Results: Following the application of the intervention, we observed a decrease in healthcare acquired *Clostridium difficile* infection rates from an annual mean of 8.76 (infections per patient-days per 10,000) in 2010 to 3.33 in 2012, and 2.23 year-to-date in 2013.

Conclusion: For achieving potential reductions, in *Clostridium difficile* infections, it is recommended that healthcare facilities adopt sociotechnical interventions aimed at assessing and enhancing current practices with hands-on education and monitoring. Additionally, we recommend the use of statistical process control as an early detection practice in hospitals.

1. Introduction

Clostridium difficile, a spore-forming, anaerobic bacterium, is one of the most prevalent healthcare acquired pathogens in the United States. Researchers estimate that there are over 300,000 cases of *Clostridium difficile* infections (CDI) per year (Yoo & Lightner, 2010). A recent study by the Centers for Disease Control and Prevention indicates that CDI has more than doubled in the last decade, replacing methicillin-resistant *Staphylococcus aureus* as the most prevalent healthcare-acquired infection (HAI) (Centers for Disease Control and Prevention, 2012). One strain of *Clostridium difficile,* ribotype 027 toxinotype III, was identified as the primary cause for the increase in prevalence. The risk of infection rises especially in immunocompromised people, the elderly, patients with long lengths of stay in a hospital, and people being treated with antibiotics such as flouroquinolones, cephalosporins, and clindamycin. Symptoms of CDI vary from watery diarrhea to pseudomembranous colitis. The severe form of CDI may require the patient to have surgical treatment (colectomy) and could lead to sepsis and death (Sunenshine & McDonald, 2006).

Transmission of *Clostridium difficile* occurs through direct contact and ingestion of bacterial spores. Spores are transmitted directly from person to person or via fomites (bed rails, linens, bed room surfaces) (Lyerly, Krivan, & Wilkins, 1988). The most common prevention measures include hand hygiene, isolation precautions, enhanced disinfection methods (use of bleach), and the use of personal protective equipment. The use of antibiotics can create unintended consequences such as increased resistance to pathogens (Carrico et al., 2013).

As defined by the literature, a case of healthcare associated, healthcare onset CDI is one that occurs more than 48 hours after admission to a healthcare facility (Carrico, 2009). The recommended treatment for infected patients is antibiotic therapy. For first time infections, with mild to moderate symptoms diarrhea and abdominal pain, the recommended antibiotic is metronidazole. Vancomycin is recommended for initial, severe infection. Fidaxomicin is normally used for recurring infections (Cohen et al., 2010; Louie et al., 2011; Sunenshine & McDonald, 2006; Sydnor et al., 2011). The effectiveness of antibiotics may be reduced with increased use, therefore it is recommended to minimize use whenever possible. In addition to the recommended treatments with antibiotics, there are now new alternatives available to fight CDI. Fecal transplants (termed fecal bacteriotherapy) have been used for many years in veterinary medicine for producing a healthy, defined gut flora. In humans, the procedure consists of transplanting the stool of a healthy person, preferably from a relative, to the patient via retention enema, colonoscopy, or nasogastric tube. Practitioners utilizing this treatment have reported a high success rate in controlling CDI (83% to 92%) (Karadsheh & Sule, 2013; Kelly, de Leon, & Jasutkar, 2012; Schleupner, 2012). However, further studies with larger populations are needed.

In late 2009, all clinical hospital staff members from LewisGale Hospital Montgomery, received online education on *Clostridium difficile* and best practices for prevention. In addition to the education, a new "isolation precautions" group and signage were developed to distinguish between contact precautions and contact enteric precaution specific to CDI. Contact enteric precautions required the use of a gown and gloves with every entry into the patient room, disinfection of equipment with bleach wipes and terminal cleaning with bleach. However, the infection prevention and other staff were concerned that the education was not being reflected in current practice at the bedside.

During 2010, the hospital saw an increase in the rates of CDI. Three clinical staff nurses working on a leadership project, partnered with the hospital's Infection Preventionist to design a series of actions whose goal was to reduce the prevalence of the infection within the hospital, and to increase healthcare worker awareness of CDI. From the outset, the project team was reluctant to introduce interventions that might cause unintended consequences, such as disrupting patient care. As healthcare workers are constantly assessing, treating, and monitoring patients throughout their shifts, the team decided that any intervention had to be tailored to fit the reality of the internal environment of the hospital. For this reason, they shifted away from traditional education interventions and focused on the assessment of current skills and practices, enhancement of those skills through hands-on learning, and corrective monitoring of prevention practices.

2. Methods

2.1 Sociotechnical intervention

A sociotechnical intervention is any action that modifies the way that personnel interact with equipment, knowledge, or the automation of the work system (Hendrick & Kleiner, 2001). Sociotechnical interventions have been used in the past in multiple areas to include construction and patient safety projects. There is a subdiscipline within ergonomics, macroergonomics, which studies the application of sociotechnical interventions in work systems. The project attempting to reduce *Clostridium dificile* prevalence did not utilize the methodology of macroergonomics, but interventions of this type could benefit from it. The hospital is currently collaborating with Virginia Tech in a study that involves macroergonomics and simulation of sociotechnical interventions.

The project team devised four different actions to deploy across the hospital. Each action was implemented after the previous one was completed, in order to avoid disruption of patient care. Throughout the intervention process, traditional medical therapy and prevention procedures continued in a normal fashion based on guidelines and evidence-based practices. Figure 1 (below) depicts the timeline for the implementation of each intervention.

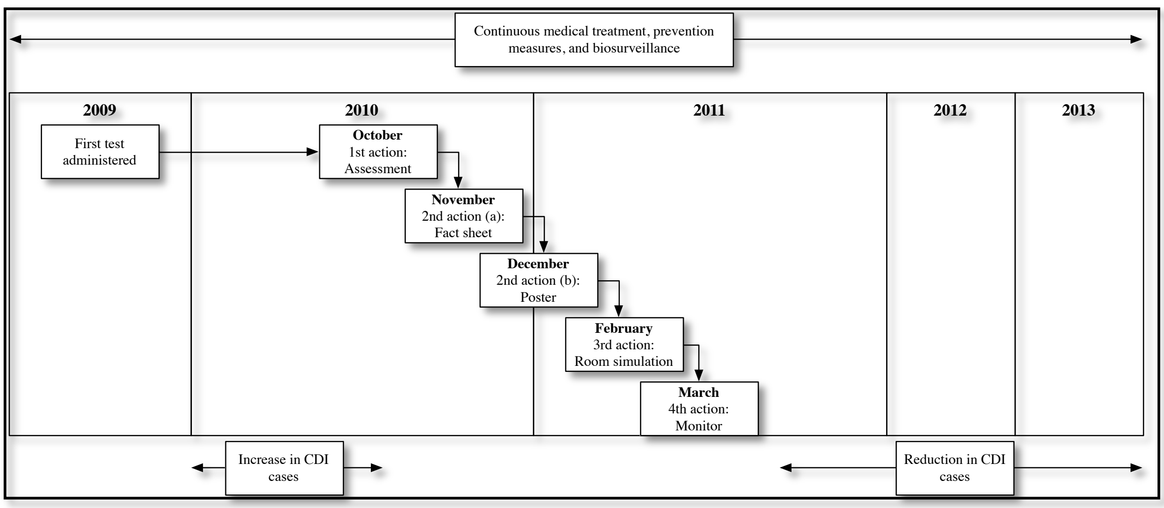


Figure 5 (Figure 1, Manuscript 1) Timeline of the intervention.

Action 1. Prevention guidelines assessment:

In 2009, the hospital's Infection Preventionist administered a test to healthcare workers to evaluate their knowledge of prevention guidelines for CDI. However, based on the subsequent increase in CDI cases, the project team decided to re-assess the staff's knowledge of those guidelines. The team randomly administered a similar test to hospital staff, to determine if prior knowledge of CDI prevention guidelines had been retained. The results indicated that the staff was still knowledgeable of the prevention guidelines. These results led the team to conclude that even though healthcare workers were aware of the guidelines, compliance during daily activities may be diminishing, and this could contribute to the change in CDI occurrence. The team decided to develop a second action that would address constant awareness of prevention guidelines throughout the hospital.

Action 2: Preventive guidelines awareness

The second action consisted of providing readily available references for CDI prevention to all hospital staff. The reference material would have to be available to healthcare workers, patients, and visitors. For this action, the project team developed a fact sheet with information about CDI. The fact sheet addressed frequently asked questions from clinical staff about CDI, but expanded to address the role of administrative, housekeeping, and ancillary services staff. This factsheet was distributed to the hospital staff. In conjunction with the fact sheet, the project team devised a poster containing CDI prevention information. The poster was designed to be easy to read and was displayed in all areas of the hospital. The poster indicated the commitment of the management team and the staff to the reduction of CDI. Both the fact sheet and the poster were placed in areas were visitors and patients could have easy access to them.

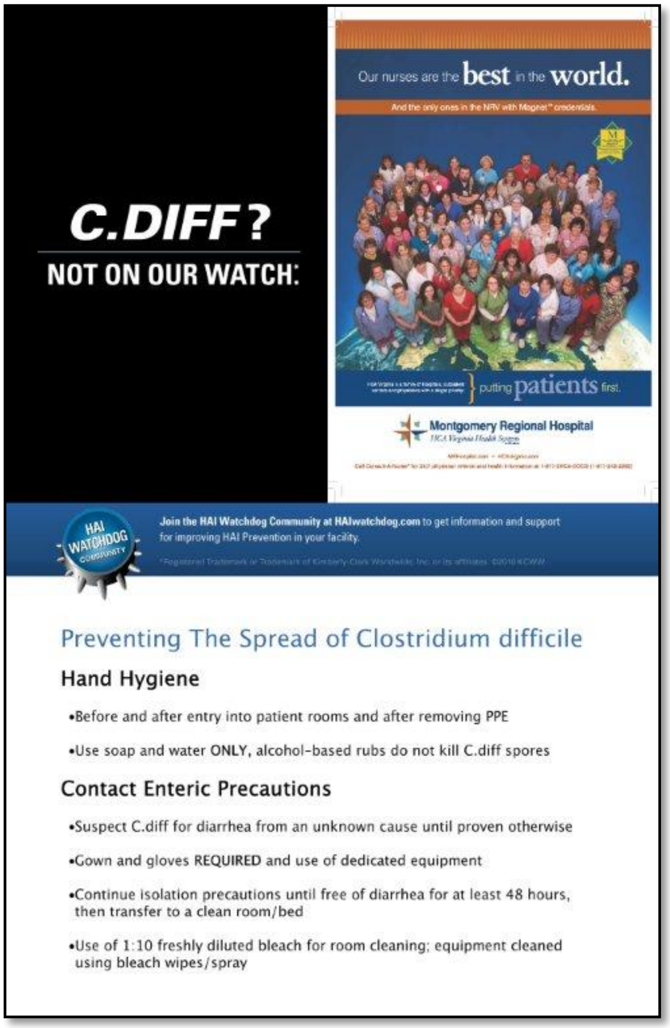


Figure 5 (Figure 2, Manuscript 1). CDI reference poster.

The poster was displayed throughout the hospital for healthcare workers, patients, and visitors.

Action 3. Healthcare training through a patient room simulation:

In addition to the reference material, the team wanted to introduce an action that would replicate the environment inside a patient's room. The objective was to demonstrate the risks of contamination in a control environment, while at the same time showing prevention precautions. The project team adapted a regular patient room to serve as a simulated *Clostridium difficile*-contaminated patient room. The team utilized Glo Germ™, a substance (liquid or powder) that mimics bacterial contamination on surfaces, and which glows under ultraviolet light. The powder form of Glo Germ™ was spread on high contamination surfaces inside the simulation room.

During the simulation scenario, hospital staff members entered the room in pairs and were asked to perform patient care activities relative to their job role. The activities included turning off the call bell, adjusting an intravenous pump, moving the patient in the bed, and assisting the patient to order a meal. The healthcare workers were asked to perform the activities in the same manner that they would during their daily activities. After the tasks were completed, the staff was scanned with an ultraviolet light. If the healthcare worker became contaminated during the simulation, the ultraviolet light would reveal Glo Germ™ on the worker. The results of the simulation ranged from minimal to mass contamination on hands and clothing.

Figure 6 (Figure 3, Manuscript 1). Mock room intervention.

Healthcare workers utilize ultraviolet light to show possible bacterial contamination during hands-on exercise.

Action 4. Prevention practices compliance:

Once the education actions were completed, the team decided to introduce a monitoring action to reinforce the progress made through the assessment and enhancement of education, and to improve compliance with prevention guidelines. The Infection Preventionist and hospital staff of each department conducted random visits to different departments within the hospital to directly observe prevention measures on patients with confirmed CDI. These observations were corrective and not punitive in nature, and the staff used this time to provide additional education if necessary. If a deficiency was encountered, the person conducting the observation addressed the non-compliant act, reminded the person of reference materials and the simulation room, and provided ways to remedy the deficiency. Direct observation continues to this date. As a result of these actions, levels of recorded hand hygiene compliance improved from 86.2% in 2009 to over 97% in 2012. Furthermore, healthcare workers displayed an increased ownership on prevention practices, and often instituted isolation based on suspicion of CDI rather than positive test results. The Infection Preventionist also received an increase in consults from healthcare workers to address concerns surrounding inpatients with known and suspected CDI. Based on the non-punitive nature of these observations, visits to other departments and measurements were not formally tracked. However, all units were provided with feedback on the improvement of compliance with best practices.

2.2 Data collection

We retrospectively collected the CDI case infection rate data for the hospital from 2009 to 2013. The case information was initially entered into a Microsoft Excel spreadsheet for infection rate analysis. The data was then statistically analyzed utilizing SAS JMP Pro 11. Patient data was de-identified by the hospital to protect patient confidentiality. The dataset used included gender, age, race, residence type such as nursing home or single family home, admission and discharge date, type of CDI (healthcare acquired, community acquired, or recurrent), and unit in the hospital. All the data for this study was used in accordance with an Institutional Review Board (IRB) protocol that was initially approved in 2011.

Positive diagnosis of CDI cases at the hospital was verified through stool samples utilizing an enzyme immunoassay test (sensitivity 94%, specificity 78%). Upon suspicion of *Clostridium difficile* infection, a stool sample was collected and submitted to the laboratory located on site, and tested.

2.3 Statistical Analysis

As recommended by the latest "Guide to preventing *Clostridium difficile* infections" (2013), we utilized statistical process control (SPC) charts to detect any changes in the prevalence of infections from 2009 to 2013 (Carrico et al., 2013). A control chart is a graphical and statistical analysis tool that is useful for prediction of data behavior. The advantage of utilizing a control chart versus another statistical tool is the ability to discriminate between natural variation, or noise, and special variation due to a particular event. A control chart can also detect significant shifts (increase or decrease) in the data that may help an epidemiologist more efficiently conduct an investigation. Control charts have been used since the 1920s in multiple industries starting with manufacturing (Benneyan, 1998b). Their flexibility and similarities to epidemiology tools make them a very useful tool for a hospital epidemiologist. In healthcare, control charts have been used to track quality of service, uniformity of procedures, cleanliness of a patient room, and disease outbreaks, among many other uses (Benneyan, 1998a). For a full explanation on the function and use of control charts, please refer to Benneyan (1998a, b).

The main variable of interest for this study is the *CDI rate*. This rate is calculated as the number of CDI cases per month divided by the number of inpatient days per month per 1,000 inpatient-days (Carrico et al., 2013). For this study we chose to utilize a denominator of 10,000 patient-days because it is the current metric in use at the hospital. In order to compare with other studies, the rates can be multiplied by '10' to obtain the previously mentioned rate.

3. Results

As mentioned in the Methods section, statistical process control charts are recommended to hospital epidemiologists as a proven graphical and statistical tool to differentiate between noise and special cause variation. In order to determine if there was a change in the infection rate since the application of the intervention, we built a control chart by plotting the monthly CDI infection rate in the hospital. Figure 4 below, depicts the CDI rate control chart. By inspection, it is possible to see a pattern in the chart that shows a lower infection rate in the latter months. When the usual Westgard and Nelson control chart tests are applied to the data, they reveal certain data points with low probability or data points that may indicate special cause variability. These rules are important because they allow the analyst or infection preventionist to detect the results that policy changes cause. An effective change in policy for infection control will produce "flags" or alerts that, allowing the infection preventionist to demonstrate the effectiveness of interventions. Policy changes that are not effective do not affect the results in the control chart and will not "raise any flags." At the same time, alerts will be triggered if a sudden increase in infection rates or other metrics occur. The control chart is an easy to use and demonstrably effective tool for epidemiology.

In April 2009, February 2010, and May 2010, the infection rate at the hospital climbed higher than two standard deviations from the mean of the data, and nearly reached the third standard deviation raising a flag for a specific rule. This rule is normally considered a warning, and the process is still considered under control. However, the analyst can exercise discretion on how to interpret the warning based on the individual characteristics of the system. Starting in September 2012, the control chart shows a flag for rule 7. Rule 7 is triggered when fifteen points or more in a row appear less than one standard deviation away from the mean on either side (Nelson, 1984). In other words, there is a special event (or intervention) that is maintaining the infection case rates in a state of limited variation. This flag is of importance to the hospital because it shows that some change occurred in prior months that have reduced the prevalence of infection. On Figure 5, we show the same data now adjusted for two separate phases. It is clear that the upper control limit has changed for the latter control points. For a description of control chart rules please refer to Nelson (1984) and Wheeler & Chambers (1992). Statistical software packages such as JMP or Minitab also provide explanations of control chart rules.

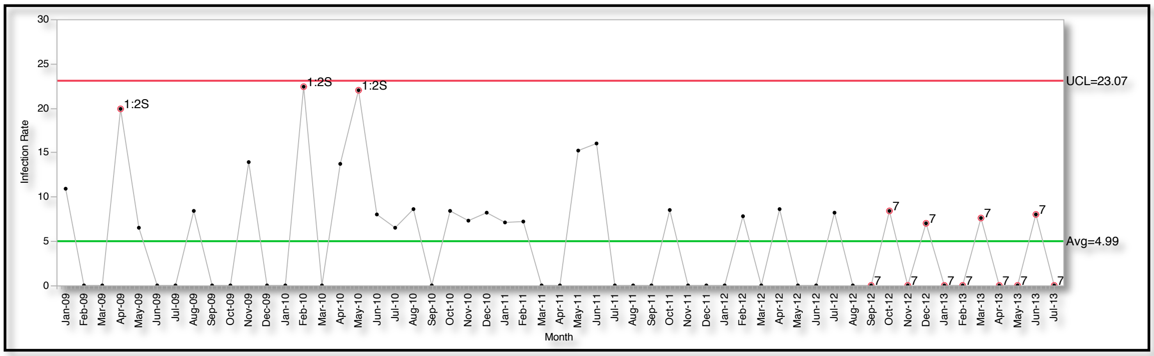


Figure 7 (Figure 4, Manuscript 1). Statistical Process Control Chart of CDI rates from 2009 to 2013.

Each dot represents the infection rate for each month. The middle line is the mean of the data provided. The top line represents the upper control limit at three standard deviations from the mean. There is no lower limit, as zero is the lowest number. Any variation in the data that is attributed to special causes is flagged. In this case, the latter rates were flagged due to a reduction in the variance.

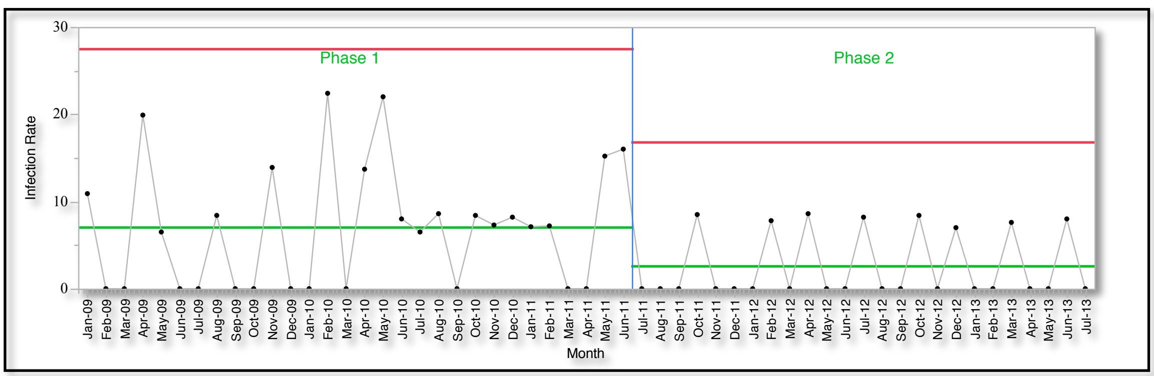


Figure 8 (Figure 5, Manuscript 1). Statistical Process Control Chart of CDI rates from 2009 to 2013 with two phases.

As a way to confirm if in fact the two phases in Figure 5 are statistically distinct, we compared the two phases. After evaluating the distribution of the infection rate we determined that it does not follow a Gaussian (normal) distribution. This is common for infection rates than tend to be skewed right higher which means that there is a higher frequency of zeroes in the distribution. For that reason, we then performed a rank sum test for nonparametric data. The two phases were found to be statistically different (p-value <0.05). Figure 6 shows boxplots of the two phases identified by the control chart. Phase 1 represents the initial state before and during the intervention. Phase 2 represents the state after the intervention. The phase 1 boxplot shows a much higher variance from the mean than phase 2. This means that before the intervention there were not only higher rates, but they were also less controlled. Phase 2 represents the output of a system that is under control on infection rates but especially on variance.

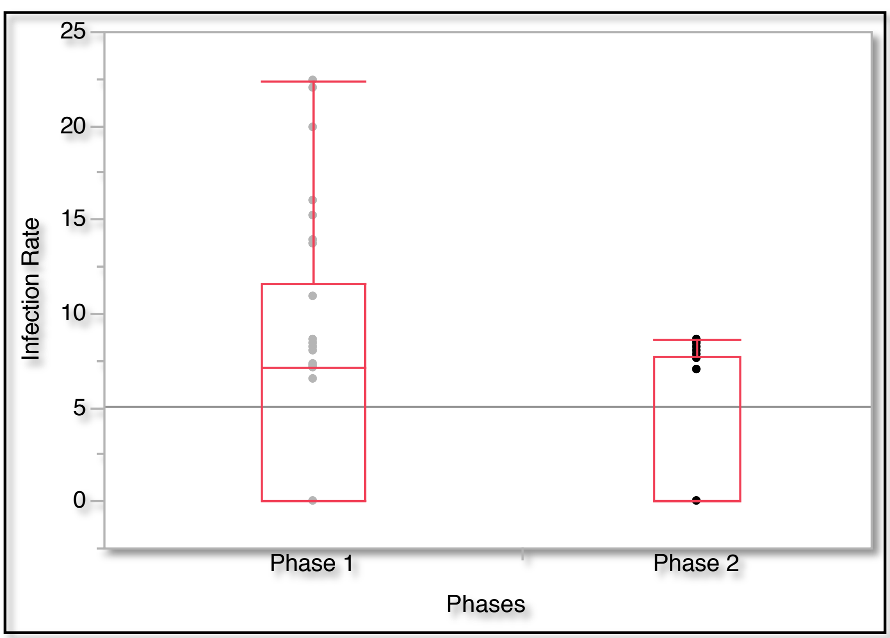


Figure 9 (Figure 6, Manuscript 1). Boxplot comparison of CDI cases before and after the intervention.

4. Discussion and Recommendations

We presented an intervention with the primary goal of reducing the prevalence of *Clostridium difficile* infections in a 146-bed hospital. Additionally, we presented a statistical analysis utilizing control charts to identify changes in the infection rate at the hospital. Statistics cannot conclusively determine that the intervention alone caused the effect observed in the control charts. However, these tools identified a change in the infection rate after the final implementation of the four actions. Furthermore, no change has been reported in the application of pharmaceutical treatment or preventive measures at the hospital. Based on those facts, we conclude that there is significant evidence linking the intervention with the reduction in CDI. Data analysis and biosurveillance of CDI should continue in the hospital to identify further changes in infection rates. It is also important to note that the actual shift in control limits for the control charts does not happen until after June 2011, even though the patient room simulation concluded at the end of March 2011. Therefore, there is a lag period of 3 months until results of the interventions can be clearly seen in the control chart. Based on that lag period, it is possible to hypothesize that other interventions may have caused the reduction in the infection rates. However, the hospital reports no other sociotechnical interventions applied before June 2011 specifically targeting CDI or HAIs. Additionally, one could theorize that any perturbation to a work system, such as an intervention, requires a time for the system to reach stability. This period could account for the lag in time. Finally, due to the number of actions that were conducted during the intervention and also concurrently with pharmaceutical treatment, it is very difficult to determine if one action was more effective than any other, or if a pharmaceutical intervention caused a further reduction. The interventions tend to confound each other when conducting a statistical analysis. One fact that is clear is that the reduction in cases has continued for two more years, discarding the possibility of random variation being the main cause of the rate improvement. Additionally, the Infection Preventionist has anecdotally experienced more interest from healthcare workers on practices that reduce the prevalence of CDI and other HAIs.

Following this analysis, we recommend that hospitals continue preventive measures and pharmaceutical treatment of patients with CDI as detailed in the prevention guidelines. Additionally, we recommend the use of education sociotechnical interventions that work around the schedule of the healthcare worker. The utilization of the simulation room is an example of an educational intervention that mimicked the actual environment in which healthcare workers perform their duties everyday. Finally, we recommend that infection preventionists assess infection rates at hospitals with the help of statistical process control. These tools are robust and proven in the healthcare environment.

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4. Manuscript 2: *Macroergonomics and simulation: a multidisciplinary methodology to design sociotechnical interventions in hospitals*

Abstract
Healthcare acquired infections (HAIs) present a growing burden for health systems. *Clostridium difficile* infections have more than doubled in the last decade. Macroergonomics provides a framework in which to design interventions to reduce the spread of HAIs. We utilized a multidisciplinary approach combining macroergonomics and simulation science to evaluate sociotechnical interventions to reduce *Clostridium difficile* infections. We evaluated the sociotechnical system inside a regional hospital utilizing the macroergonomics framework and determined appropriate interventions. We simulated hospital workers as agents performing over 13 million activities as well as over 2 million contacts among them. We additionally observed a 15% reduction in simulated infections through patient isolation, as well as a 10% reduction through antibiotic restrictions, both compared to a control alternative. Reduction in patient contacts with infected surfaces is very important in reducing infections. The combination of macroergonomics and simulation is an effective method to evaluate hospital policies and interventions.

Key words: Macroergonomics, simulation, healthcare acquired infections, systems engineering

Practitioner Summary
The objective of this study is to identify sociotechnical interventions to reduce healthcare acquired infections. A multidisciplinary approach was utilized combining macroergonomics and high performance simulation. Contacts with contaminated surfaces were responsible for the largest number of infections. Isolation of community-acquired cases provided the best results as an intervention.

1. Introduction

1.1 Macroergonomics

Macroergonomics is a sub-discipline within human factors and ergonomics (HF/E) that is concerned with the life cycle of work systems (research, analysis, design, development, and evaluation). A work system is defined as any human activity within a sociotechnical system, which is in turn characterized by the relationships between individuals, technology, organizational structure, internal environment, and external environment. The more commonly known microergonomics (or hardware ergonomics) approach is interested in how the human-machine system interacts. Macroergonomics takes a more systemic approach, looking at how multiple subsystems influence each other and the entire work system in a human-centered approach (H. W. Hendrick, 2002; H.W Hendrick & Kleiner, 2001).

Macroergonomics seeks to optimize the work system in three different ways. It utilizes a top-down approach to evaluate the overall work system and its variables. Macroergonomics also involves the subsystems' end-user in its optimization through techniques like participatory ergonomics in a bottom-up approach. Finally, parallel subsystems are jointly optimized in a middle-out approach (H.W Hendrick & Kleiner, 2001). The advantages of the macroergonomics process have been extensively documented and tested (Buckle et al., 2010; Haro & Kleiner, 2008; H. W. Hendrick, 2003). Intangible benefits of macroergonomics include increased employee participation and output, increased communication between subsystems, and reduction in safety hazards (H. W. Hendrick, 2003).

Analysts have developed multiple models for the application of macroergonomics (H.W Hendrick & Kleiner, 2001) to include multiple applications in healthcare (Carayon et al., 2006; Karsh & Brown, 2010). For this study we utilized the Macroergonomics Analysis and Design (MEAD) framework. MEAD follows 10 specific steps: scanning analysis, system type and performance analysis, technical work process analysis, identifying variances, creating the variance matrix, creating the key variance control table and role network, function allocation and joint design, responsibility perception analysis, designing/redesigning support sub-systems and interfaces, and implementing, iterating and improving (H.W Hendrick & Kleiner, 2001; Kleiner, 2006).

1.2 Clostridium difficile

In the span of a decade (2000-2009), *Clostridium difficile* infection (CDI) cases have more than doubled in the United States and primary diagnosis of CDI has more than tripled. Additionally, the onset of CDI has extended to the place of residence of the patient to include nursing homes ("Vital signs: preventing Clostridium difficile infections," 2012). It is estimated that the cost of treating one patient could be as high as $24,400 (Lucado, Gould, & Elixhauser, 2012).

Clostridium difficile is a naturally occurring bacteria in the intestinal flora of every person (Karen & John, 2011). A hypervirulent strain of the bacteria, designated as NAP1/B1/027, has been identified as responsible for the current outbreak. When antibiotics, such as fluoroquinolones, are used to treat other conditions in the patient, the bacteria can overpopulate and release toxins into the intestine. This overpopulation of *Clostridium difficile* can produce multiple symptoms such as diarrhea and abdominal pain. In severe cases, patients experience pseudomembranous colitis and sepsis. In some cases it can be fatal. Additionally, there is a high rate of disease relapse (15-35%) (Cohen et al., 2010; Lyerly, Krivan, & Wilkins, 1988; Sunenshine & McDonald, 2006). Risk factors regularly associated with *Clostridium difficile* infection include being 65 years-old or older, suffering a severe underlying illness, prior use of antibiotics, and long hospital stays (Bignardi, 1998; Sunenshine & McDonald, 2006).

Clostridium difficile spreads in a hospital setting through direct contact with patients. The best way to prevent spread of *Clostridium difficile* in a hospital setting is to adhere to prevention measures such as hand washing, isolation precautions, and appropriate room cleaning (Carrico et al., 2013). Hospitals have reported reduction in infection rates by utilizing protocols that include hand hygiene, extended disinfection, and isolation, as well as educational interventions for healthcare workers, patients, and visitors (Abbett et al., 2009; Whitaker, Brown, Vidal, & Calcaterra, 2007). The most common pharmaceutical therapy for *Clostridium difficile* is the use of antibiotics such as metronidazole, vancomycin, fidaxomicin, or bacitracin depending on the stage of the infection (Tomkins, Raynor, Rothwell, DeSilva, & Wilson, 2011; Yoo & Lightner, 2010).

1.3 Highly detailed Simulation of Healthcare Acquired Infections

Simulation and modeling of disease outbreaks is not a new concept. Models and simulation differ in that a model is a simplified representation of reality, whereas simulation is a way to understand the model's behaviour, especially for specific scientific questions. Thousands of models have been used in the past to understand the behavior of pathogens in the environment and in hospitals. The first modern epidemiological model (Susceptible, Infected, Removed) was developed by Kermack and McKendrick in 1927

(Kermack & McKendrick, 1991). This model has been the basis for most modern simulations in disease outbreaks. It is important to point out that no model is completely correct nor can it fully represent the true complexities of reality. However, simulations (especially complex simulation) can provide deep insight to real world problems in the realm of infectious diseases.

There are multiple types of simulation models and methods (Keeling & Rohani, 2008). We utilized EpiSimdemics as the simulation software for our study. EpiSimdemics is an advanced, scalable computer algorithm used to simulate the spread of infectious diseases over extremely large contact networks. EpiSimdemics was developed with the objective of studying sociotechnical interventions on populations during epidemic and pandemic scenarios. Prior studies have utilized this tool for analysis of large populations at a scale of 100,000,000 people (Barrett, Bisset, Eubank, Feng, & Marathe, 2008; Keith R. Bisset et al., 2012; Keith R. Bisset, Feng, Marathe, & Yardi, 2009). EpiSimdemics combines the development of synthetic populations with stochastic, finite state machines and social network theory. Synthetic populations are developed in a bottom-up approach by obtaining real world data, or in the case of this study, from electronic medical records and observations. The synthetic agents in the simulation were placed into a social network that includes every contact with other agents, the duration of every contact, and the location of the contacts. Finally, the social network flows through a finite state machine that describes the different health states of a particular disease and the parameters of the disease (Barrett et al., 2008).

The rapid adaptability of simulation can help reduce the uncertainties of dynamic change in a hospital. Simulation can help develop innovative ways to attack a very complex problem in an efficient manner. First, simulation can test the application of individual interventions or groups of interventions. Secondly, simulation has the ability to test interventions on specific populations. This practice could be considered unethical for clinical practice, but is perfectly safe on an *in silico* population. Lastly, simulation approaches can help avoid the system disruption that other "real world" interventions may cause. For this reason, expensive or impractical interventions can be tested relatively easily and quickly.

The objective of this study is to identify sociotechnical interventions to reduce HAIs, specifically *Clostridium difficile,* in healthcare facilities.

2. Methods

2.1 Data Collection

We collected data from a regional hospital in southwest Virginia in multiple forms. First, we obtained one year of patients' hospital visits information in the form of electronic medical records. These records included the time and date of admission, time and date of discharge, locations (room and unit), diagnosis, treatment, and patient demographics. The patient information was de-identified by the hospital to protect patient confidentiality. Over 30,000 patients were included in the study. There were no exclusion criteria for the patients.

In addition to the patient information, we collected healthcare worker information by conducting direct observations or "shadowing." The first author followed over 30 different healthcare workers as they conducted their daily activities. These observations lasted from 4 to 8 hours and were conducted during normal operations in the hospital. No personal information was recorded to protect the privacy of each patient and healthcare worker. The information collected included the daily duties, locations, and person-to-person contacts for each class of healthcare worker. Finally, the first author also collected information about the patient rooms, hospital layout, healthcare workers' lounges, and hospital visitors. All the information collected from the hospital was placed into a secure SQL database and used as the main inputs for the hospital simulation. All data was requested, approved, and obtained through the hospital's Institutional Review Board.

2.2 MEAD Process

This study followed the MEAD methodology as its framework to develop sociotechnical interventions. Each step of the MEAD process was conducted by the first author and reviewed by healthcare workers at the hospital. The adaptability and flexibility of macroergonomics and the MEAD process allows it to be combined with multiple frameworks. We conducted the MEAD analysis in conjunction with known continuous improvement and simulation tools. (Table 1) lists the 10 steps of the MEAD process and describes how each step was accomplished for our methodology with the assistance of computer simulation. This article will not go into the detail of each step of the MEAD process, as this has been accomplished in many other works, however, we will discuss the main phases in the methodology.

Table 1 (Table 1, Manuscript 2). MEAD methodology in combination with simulation.

MEAD Steps	Sub phases analysis (How was this step achieved?)	Implementation
1. Scanning analysis 1.1 Perform mission, vision, principles analysis 1.2 Perform system scan 1.3 Perform environmental scan 1.4 Specify initial organizational design dimensions	1.1 Mission, vision, principles (MVP), and objectives are defined and documented by the hospital and provided to all employees. 1.2 Supplier, input, process, output, and customers (SIPOC) diagram for the hospital (figure 2). 1.3 Regulations established by Centers for Medicare & Medicaid Services (CMS) and the Joint Commission. Additional standards from professional associations, e.g. Association for Professionals in Infection Control. 1.4 Hospital organized by units. Level of complexity, centralization, and formalization for the hospital.	Data collection, continuous direct observations, environmental scanning.
2. System type and performance analysis 2.1 Define production system type 2.2 Define performance expectations 2.3 Specify organizational design dimensions 2.4 Define system function allocation requirements	2.1 Production/service system for each hospital unit (example of ICU process figure 2). 2.2 Healthcare system expectations and key performance metrics cascade from regulations and Hospital's MVP. Monthly, quarterly goals established, e.g. rate of healthcare acquired infections in the ICU. Quality checkpoints established by unit, e.g. hand washing compliance. 2.3 The unit's levels of complexity, centralization, and formalization vary widely. The rigidity of procedures in the operation room vary greatly from the more relaxed room cleaning procedures or food delivery. 2.4 Function allocation specified by clinical protocol and regulations.	Data collection, continuous direct observations, environmental scanning.
3. Technical work process analysis 3.1 Identify unit operations 3.2 Flowchart the process	3.1 Shadowing of healthcare workers in each unit. Schedules/shift information. 3.2 Creation of flowcharts per healthcare type.	Data collection, continuous direct observations, environmental scanning.
4. Identifying variances 4.1 Collect variance data 4.2 Differentiate between input and throughput variances	4.1 *Clostridium difficile* rates, cases, and demographics from 2009 to 2013 collected from hospital. 4.2 Use of statistical process control charts to diferentiate normal vs. special cause variances.	Subsystem's variables measurement, variance analysis, cause and effect analysis
5. Creating the variance matrix 5.1 Identify relationships among variances 5.2 Identify key variances	5.1, 5.2 Development of variance matrix, and Ishikawa (cause & effect) diagram	Subsystem's variables measurement, variance analysis, cause and effect analysis
6. Creating the key variance control table and role network 6.1 Construct the key variance control table 6.2 Construct the role network 6.3 Evaluate effectiveness 6.4 Specify organizational design dimensions	6.1 Variance control table 6.2, 6.3, 6.4 Role network, social contact network for simulation	Subsystem's variables measurement, variance analysis, cause and effect analysis
7. Function allocation and joint design 7.1 Perform function allocation 7.2 Design technological subsystem changes 7.3 Design personnel cahnges 7.4 Prescribe final organizational design	7.1, 7.2, 7.3, 7.4 Assignment of daily tasks to in-silico population through sequences matrix in the information creator program	In-silico information creator, intervention evaluation, simulation
8. Responsibility perception analysis 8.1 Evaluate role and responsibility perceptions 8.2 Provide training support	8.1, 8.2 Assignment of roles through template matrix in the information creator program	In-silico information creator, intervention evaluation, simulation
9. Design/redesign support sub-systems and interfaces 9.1 Design/redesign support subsystems 9.2 Design/redesign interfaces and functions 9.3 Design/redesign the internal physical enviroment	9.1, 9.2, 9.3 Changes in subsystems/units in simulation	In-silico information creator, intervention evaluation, simulation
10. Iterate, implement and improve 10.1 Implement 10.2 Perform evaluations 10.3 Iterate	10.1, 10.2, 10.3 Simulation iteration, interventions analyses, public health analysis methods	In-silico information creator, intervention evaluation, simulation

Step 1 of the MEAD process is the initial scanning of the entire hospital system (external, internal, and subsystems) to understand its objectives, processes, and procedures. In order to complete this step, we obtained information about the internal and external environment. The external environment is represented by healthcare regulations and standards, and by the community that surrounds the hospital. In the external environment there are two main bodies that provide specific and objective measurements for hospitals: the Centers for Medicare & Medicaid Services (CMS) and the Joint Commission. The Joint Commission is an independent institution that provides standards of practice and certifications for healthcare facilities in the United States (The Joint Commision, 2013). The CMS is the government agency in charge of Medicare, Medicaid, the Children's Health Insurance Program, and the Affordable Care Act's Health Insurance Marketplace (Centers for Medicare and Medicaid Services, 2013). Actions in the external environment affect the hospital's operations and level of service.

The internal environment in the hospital consists of technology, personnel, and organizational structure. The internal environment of the hospital is surrounded by a boundary that allows the transfer of information and technologies. The main purpose of the hospital is to provide the highest level of quality care to the patients. The personnel subsystem consists of healthcare workers, patients, and visitors. The technological subsystem includes the clinical knowledge and expertise of the healthcare workers, as well as the hardware and machine automation that allows for treatment of patients. Moreover, the internal system also includes the work units within the hospital. Examples of work units include the intensive care unit (ICU), the operating room (OR), and the emergency department. Each one of these work units has its own characteristics, procedures, and goals. Figure 1 is a depiction of the hospital system and its subsystems.

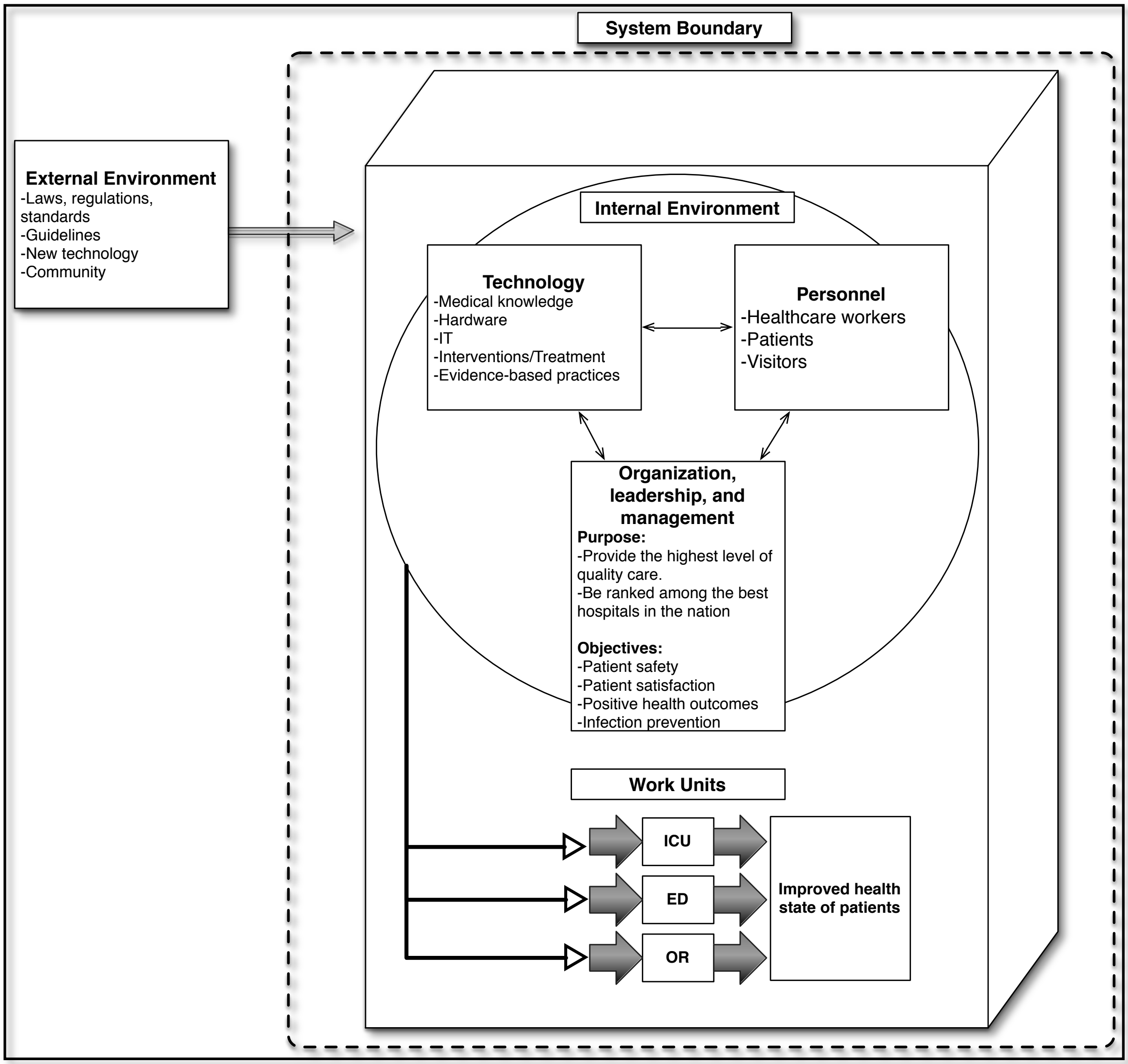


Figure 10 (Figure 1, Manuscript 2). Subsystems diagram of the hospital.

Phase 2 of MEAD involves the analysis of the system and its performance. This phase of the study was completed through electronic data collection and direct observation of healthcare personnel at the hospital. Based on the standards issued by CMS and the Joint Commission, the hospital aims to be ranked among the nation's top hospitals in core measures such as heart attack or chest pain process of care, surgical care improvement, heart failure process of care, and pneumonia process of care. Additionally, infection control and patient safety are placed among the highest priorities for the hospital. The hospital general objectives are the basis for the performance criteria for each of its work units. Objectives are evaluated on a monthly and quarterly basis. Additionally, each work unit varies greatly in organizational structure. For example, the operating room (OR) and the emergency department (ED) are very decentralized compared to other departments. The ED and OR conduct their own scheduling functions, have specialized personnel, and have strict and detailed procedures when it comes to infection prevention.

Phase 3 in the MEAD process is concerned with the analysis of the technical work. For this phase, we constructed flowcharts and vignettes that detailed the daily activities of every type of healthcare worker in the hospital. Each flowchart and vignette was then converted to computer code and utilized as input in the hospital simulation. (Appendix 1) depicts a SIPOC (Suppliers, Inputs, Process, Outputs, and Customers) diagram of the ICU operations.

We completed Phase 4, 5, and 6 of the MEAD process by obtaining *Clostridium difficile* infection rate information from the hospital for the period of five years (2009-2013). For each year, we identified variances through the use of Statistical Process Control (SPC) charts. SPC charts help the analyst assess whether variance in a process was caused by random variation or by special causes. We developed another research article that describes the infection rate variance data and the use of control charts to identify it (Jimenez, Coluni, et al., 2013). In addition to the SPC chart analysis, we created a variance matrix and identified sources of variance utilizing a cause and effect diagram. As part of phase 6 on the MEAD process, we developed a key variance control table and established a role network for all the healthcare workers in the hospital.

Phase 7-10 of the MEAD framework were achieved through highly detailed simulation. We developed a template of all of the roles of healthcare workers in the hospital. This template is later used as an input for the simulation program. One of the advantages of these files is that they can be tailored for specific interventions. Changes in subsystems or units in the simulation are easily achieved by changing the template data and uploading it into a database. Finally, each experiment in the simulation was iterated 100 times for a duration of 200 days (each day iterated 100 times). We completed the analysis of interventions with commonly used public health and epidemiology methods. Based on the MEAD process and the applicability to the simulation, we decided to evaluate five different intervention scenarios using the simulation. These scenarios are described in (Table 2). One of the advantages of simulation is the ability to evaluate scenarios that are infeasible, impractical or even unethical to replicate in a real setting. In this case we created two scenarios that would be considered unethical to perform on real patients (no treatment and antibiotic restriction). Their use in a simulated environment can provide insight into the use of antibiotics, and as a basis of comparison for other scenarios.

Table 2 (Table 2, Manuscript 2). Description of sociotechnical scenarios.

Scenario name	Scenario description
No treatment	No pharmaceutical or preventive treatment provided.
Patient isolation	Complete adherence to isolation precautions for community-acquired CDI patients.
Hand washing	Complete adherence to hand washing procedures during visits to patient rooms. Hand washing when entering and exiting the patient room.
Targeted room cleaning	Bleaching of all major room surfaces of community-acquired CDI patients during their stay at the hospital.
Antibiotic restriction	No dispensing of antibiotics to patients for their chief complaint before being tested for CDI.

2.3 Development of the Hospital Simulation

The methodology of developing synthetic populations for hospitals, disease models, and conducting experiments with hospital simulations has been documented in prior studies (Jimenez, Lewis, & Eubank, 2012; Jimenez, Lewis, & Eubank, 2013). We provide some of the details in this section. We developed a synthetic population representing the entire hospital population (patients, healthcare workers, and visitors) from the data initially collected. Our population was built at the individual level through the use of a population builder program written in Python 2.7 computer language. The individuals were then combined at hospital unit level (bottom-up approach), and finally at the whole hospital level. The population represents all the movements and contacts that patients, healthcare workers, and visitors experience during 200 days. Additionally, we developed synthetic versions of some of the most important fomites known in the literature to transmit the *Clostridium difficile* infection. (Table 3) shows the detail of the hospital synthetic population. In order to start the spread of the infection in the synthetic population, we initially infected those patients that arrived at the hospital with a community-acquired infection.

Table 3 (Table 3, Manuscript 2). Hospital population details.

Type of agent-person	Number
Patients	30,294
Healthcare Workers	431
Visitors	12,715
Patient room surfaces	998
Total number of agents	44,438
Hospital Units	21
Hospital Floors	4
Hospital Rooms	231

After developing the synthetic population, we created a disease model for *Clostridium difficile.* The disease model is a finite state machine (FSM) in which individual agents progress through multiple health states as the infection progresses or recedes. A review of literature determined all the parameters in the model (Carrico et al., 2013; Cohen et al., 2010; Karadsheh & Sule, 2013; Sunenshine & McDonald, 2006). Figure 2 is a depiction of the disease model and the disease parameters. In the disease model, the transitions from one health state to another represent sociotechnical interventions (pharmaceutical or non-pharmaceutical treatments). For this simulation we did not utilize the fecal transplant or surgery as interventions, as they are not normally practiced in the hospital we are representing. However, it is important to understand that these could be added to the list of interventions.

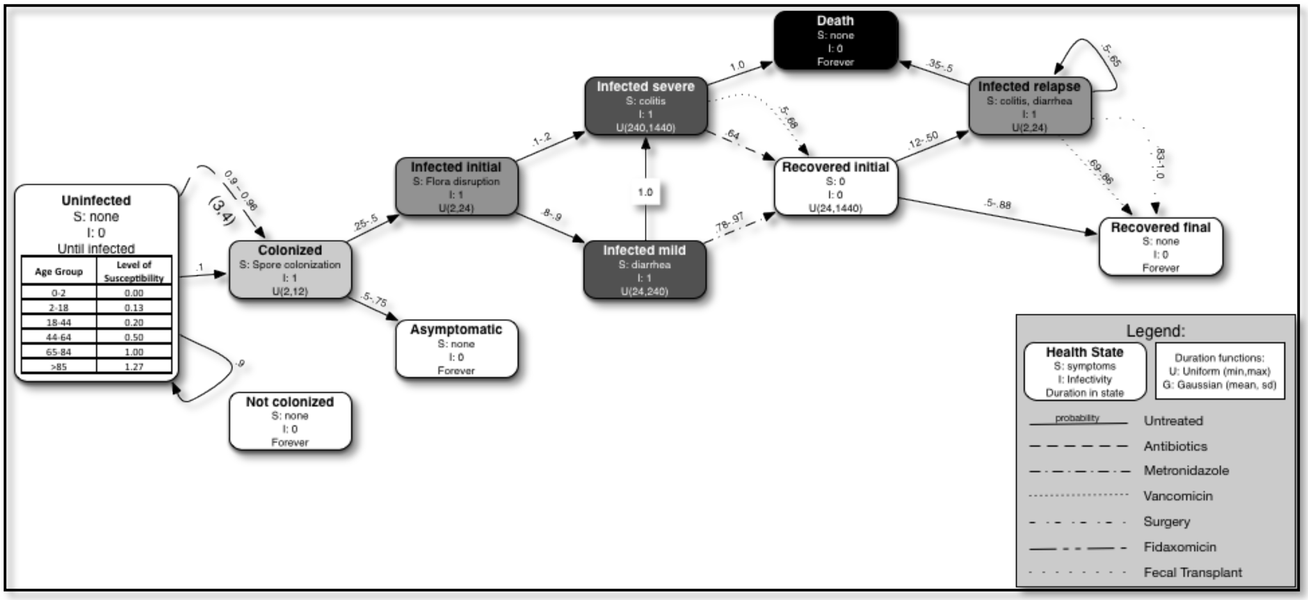


Figure 11 (Figure 2, Manuscript 2). Disease model for patients, visitors, and healthcare workers.

Each square represents a health state, and every arrow represents a transition between states (specific treatment or intervention).

We developed five different testing scenarios to evaluate based on the interventions obtained during the macroergonomic analysis. These interventions serve as the experimental factors for our study. The first scenario (no treatment) served as the calibration for the simulation. We utilized this scenario to adjust infectivity and susceptibility parameters for each health state in the disease model so that it would match the real world number of infections. The second scenario is a control in which no sociotechnical interventions are applied to the infection at the hospital. The rest of the scenarios evaluate combinations of interventions. Each scenario was simulated for 200 days, and was repeated for 100 iterations. The details of each scenario are presented in (Table 2).

2.4 Model Validation

The validation of the simulation was achieved through collaboration with the hospital and through the calibration of the simulation against the known number of hospital acquired infections. We first demonstrated model validity based on the construction of the model. We obtained the most detailed data available describing the movement of patients through the hospital. Additionally, the healthcare worker, visitor, and fomite behaviors were obtained through direct observations at the hospital. Face validity of the model was achieved through collaboration with the hospital Infection Preventionist and other healthcare workers. The hospital Infection Preventionist agreed that the dynamics of the simulation behaved in a similar manner to the actual movements of patients and healthcare workers during normal hospital operations.

We initially calibrated the simulation model with information from a retrospective chart review of community-acquired infection cases at the hospital. We obtained the patient number, location, and time of arrival to the hospital. The information on community-associated cases from the chart review was utilized to seed the simulation. Utilizing the community-associated cases is an acceptable assumption because these cases are the original source of infection in the hospital.

3. Results

As discussed in the methods section, we utilized a population builder to develop the hospital population based on patient records and hospital observations. The population builder assigned over 13 million activities to all the agents in the simulation. These activities included patient visits to the hospital, healthcare worker activities, hospital visitor activities, and fomite contacts with human agents. We also observed over 2 million agent-to-agent contacts during the 200 simulated days. Figure 3 shows a representation (sociogram) of all the agents (depicted as spheres or nodes) and their contacts (depicted as lines or edges). The social network is a constant throughout the multiple simulations (i.e. day 32 on scenario 2 has the same activities and contacts as day 32 on scenario 6). By having the same activities duplicated for each scenario, we can have a one-to-one comparison of interventions.

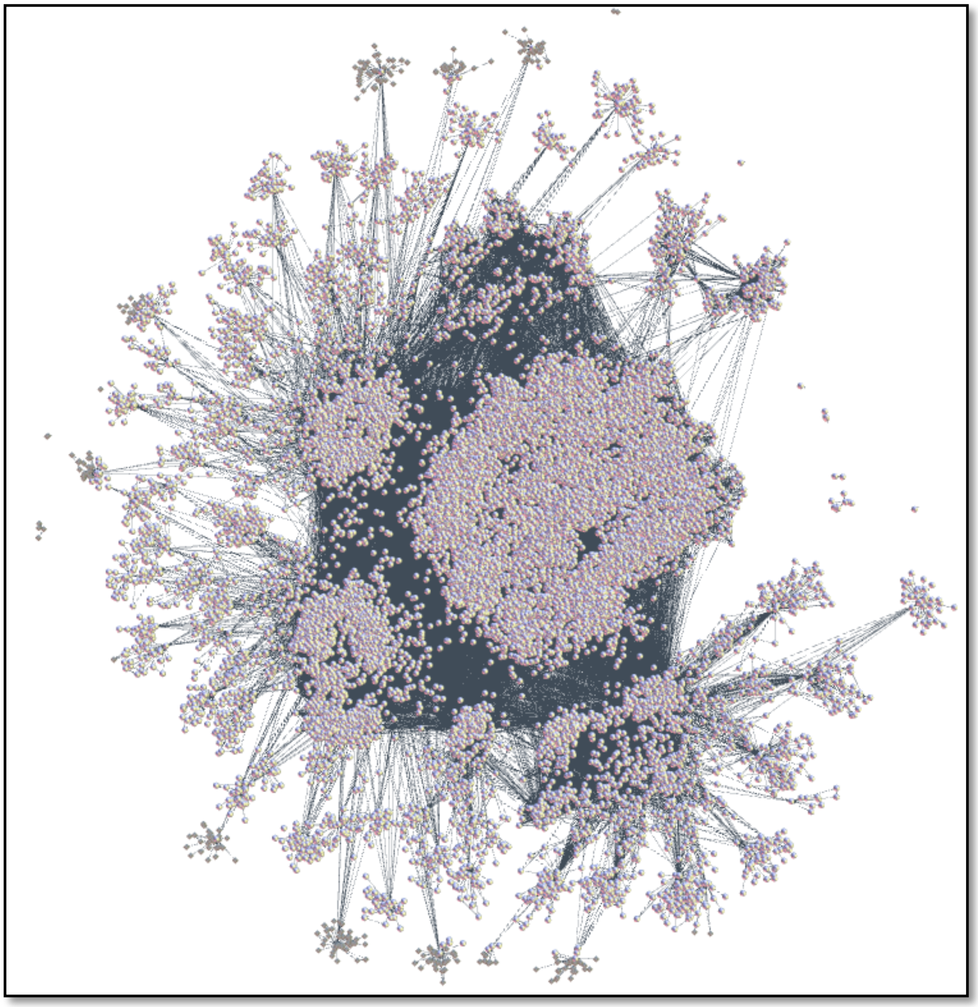


Figure 12 (Figure 3, Manuscript 2). Social network diagram or sociogram of the hospital population.

Spheres or nodes represent agents. Edges or lines represent contacts between agents. Two or more agents have to be in the same location, at the same time to be considered in contact. These contacts represent possible exposure if one of the agents is infected with CDI. Clusters of nodes represent units within the hospital.

We conducted simulations on five different intervention scenarios. Figure 4 shows the cumulative average numbers of infections per scenario. Each curve represents the average of 100 iterations per scenario. Patient isolation was the most successful scenario with an average of 34 infections, followed by antibiotic restriction with an average of 35 infections. The "no treatment" intervention had an average of 39.4 infections. For each of the scenarios, we analyzed the daily number of infections to determine if they were significantly different from each other. We first determined that our data does not follow a Gaussian distribution (as is common with infection data), and required a different statistical method to determine if the interventions were different to one another. We analyzed the data using a Wilcoxon rank test to compare pairs of each of the scenario datasets. Most scenario comparisons were found to be statistically distinct from one another (p-value < 0.05), with the exception of targeted bleaching, hand washing and antibiotic restrictions (p-value > 0.05). Furthermore, we observed that contaminated room surfaces were the type of agent that exposed patients the most to CDI, followed by other patients.

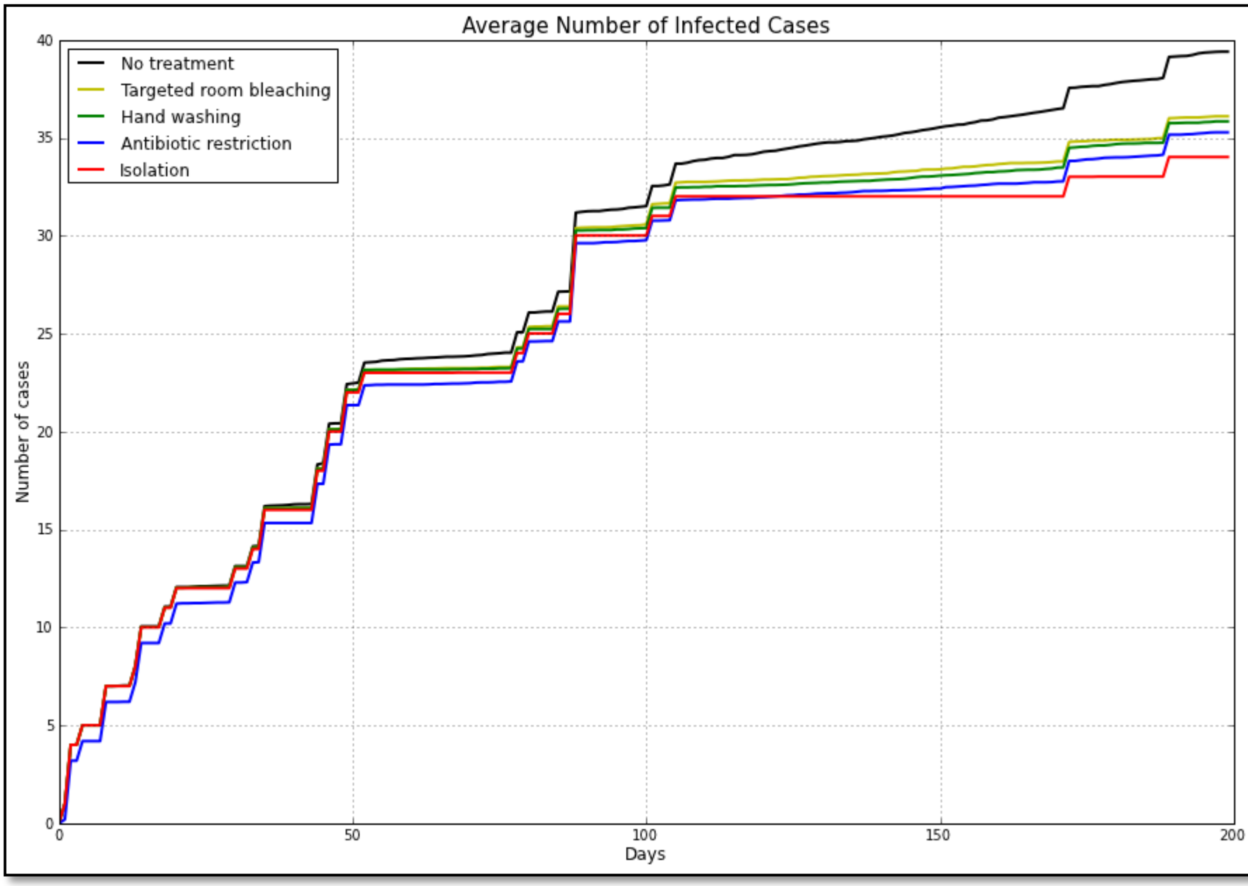


Figure 13 (Figure 4, Manuscript 2). Comparison of scenarios.

Each curve represents the cumulative sum of average infections per day of simulation. Infected patient isolation proved to be the most effective prevention intervention, followed by antibiotic restriction.

4. Discussion

We developed a simulation of the entire population of a regional hospital in order to evaluate different interventions to reduce infections. The difference between this study and other hospital simulations is multifaceted. First, this study utilizes a multidisciplinary approach combining macroergonomics, public health, and simulation. We completed a detailed study of the hospital following the MEAD framework, then we developed interventions based on the findings, and finally we evaluated the interventions with simulation. This methodology thus bridges the gap between development of interventions and evaluation. Furthermore, we created highly detailed activities of multiple types of agents including patients, healthcare workers, hospital visitors, and patient bedroom surfaces. This level of detail allows us to specify the activities for each agent down to seconds. For this reason, and due to the amount of information created, we utilized high performance computing to complete the study. The simulation software and methodology has been used in the past for larger studies at the regional and national level. This is the first time that this software has been utilized for interventions at the scale of a hospital.

We observed that different interventions reduce the spread of CDI throughout a hospital. Patient isolation was the most effective intervention according to the simulation results. This intervention consisted of identifying the patients diagnosed with community acquired CDI and reducing the ability for patients to infect other agents. The motions of other agents throughout the hospital remained the same, to include direct contacts with healthcare workers, visitors, and bedroom surfaces. Compared to the control intervention, patient isolation reduced cases by 15%. The next intervention, in order of infection reduction, was antibiotic restrictions. This type of intervention would be impossible to reproduce in a live hospital environment, as patients cannot be denied antibiotics when they have an infection. We were able to observe a reduction of 10% in cases. Adherence to hand washing is one of the most emphasized interventions throughout the literature. Even with 100% compliance, we were able to observe just an 8% reduction in cases compared to the control scenario. Hospitals have tried to control hand-washing procedures, however, compliance is difficult to measure and reporting is not very accurate. For this scenario we assumed that all healthcare workers followed hand-washing precautions as expected. Finally, we also observed an 8% reduction in cases by conducting targeted bleaching of rooms that had patients that were diagnosed with community-acquired CDI. For our simulation, contaminated room surfaces were the top source for infection exposure. Room surfaces that are in direct contact with the patient have more time to become contaminated with *Clostridium difficile* from an infected patient. If they are not cleaned properly, these surfaces can infect the next patient that enters the room.

Even though mortality and morbidity are high among patients, the level of infectivity of *Clostridium difficile* is very low. *Clostridium difficile* is still considered a very rare disease. We observed that even in the worst-case scenario, the number of cases does not climb very high. The infection rates actually experienced by the hospital have remained under control for the last 2 years and are extremely low. This reflects on the hospital's efforts to reduce HAIs. It is important to remember that even one case of CDI represents a high cost in treatment for the hospital. Any reduction in infection rates is important for the hospital and for the community that it serves. As mentioned before, hospitals are not stand-alone entities and federal regulations and local and state laws also govern the way that hospitals conduct their operations. As determined by regulations from CMS, hospitals are required to cover the cost of treatment for HAIs. This can be interpreted as an interaction between the external and internal subsystems and described earlier.

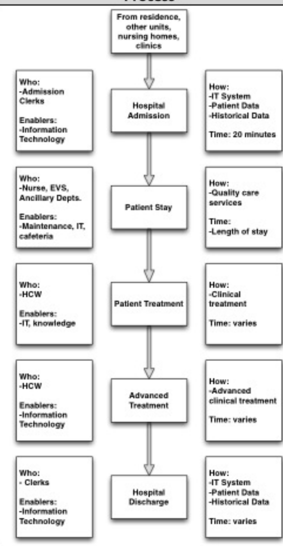
One of the limitations of this study is that simulation can never be perfect. Many different types of interventions can be developed for simulation, but not all interventions can be replicated with our methodology. Furthermore, we utilized a "normal day" approach for healthcare worker activities based on the data that we gathered. Special situations that do not follow a "normal day" could change the way that agents interact in the simulation creating more or less contacts with a patient. Finally, one important assumption in this study is that healthcare workers follow all infection precautions with full compliance. We understand that this is not always the case, but we also recognize that healthcare workers are extremely professional and strive to reduce the risk of infections in patients. In simulations of this kind we are comparing the best outcomes that could be expected under each intervention.

5. Conclusion

We presented a multidisciplinary approach to evaluate sociotechnical interventions in a hospital. We performed a macroergonomics analysis to determine the best interventions to evaluate. The interventions were compared to each other using highly detailed simulation. We were able to demonstrate that isolation was most successful in reducing the number of infections compared to the control. Other interventions were also successful, but their effects are not significantly different from each other. The combination of macroergonomics analysis and highly detailed simulation is a very effective way to compare multiple interventions in a relatively fast and inexpensive manner, but above all without perturbing the daily operations of a busy hospital. We believe that this combination of methods will prove to be an invaluable asset to healthcare workers seeking to reduce healthcare acquired infections.

Appendix 1

Table 4. SIPOC diagram of the ICU.

<table>
<tr><th>Supplier</th><th>Inputs</th><th>Process</th><th>Outputs</th><th>Customer</th></tr>
<tr>
<td>Personnel:
-Patients: waiting rooms, PCU, OR, ED, nursing homes, clinics.
-Healthcare workers: training programs, local colleges
-Visitors: local region.
Technology:
-Hardware: Information Technology, maintenance, medical equipment dept.
-Materials and supplies: medical suppliers, maintenance, laundry, medical device suppliers, lab.
-Medical treatment/knowledge: research, medical guidelines, clinical trials, collaborating institutions
Policies:
-Management
-Regulatory agencies
-Government
Internal Environmental information:
-Management
-Other work units
-Lab
-Information Technology System
External Environment information:
-Work unit
-Regulatory agencies
-Professional organizations
-Collaborating institutions</td>
<td>Personnel:
-Patients
-Healthcare workers
-Visitors
Technology:
-Clinical knowledge
-Hardware
- Information Technology
-Materials and supplies
-Medical treatment/knowledge
Policies:
-Laws and regulations
-Internal rules and regulations
-Guidelines
-Procedures</td>
<td>
</td>
<td>Intended
Personnel:
-Healthy Patients
-Satisfied healthcare workers
Technology:
-Hardware use and wear
- Information Technology
-Materials and supplies
-Increased experienced, medical treatment/knowledge
Policies:
-Evidence-based practices
-Continuous improvement

Unintended
Personnel:
-HAIs on patients or healthcare workers
-Burnout on healthcare workers
Technology:
-Hardware use and wear
- Improvement of Information Technology
-Waste of materials and supplies
Policies:
-Unintended errors
-Deviation from policies and protocols by staff, patients, visitors
-Policy improvement by emergence</td>
<td>Personnel:
-Patients: other units within the hospital, outside healthcare facilities, community

Technology:
-Hardware: Information Technology, maintenance, medical equipment dept.
-Materials and supplies: waste, maintenance, laundry, lab.
-Medical treatment/knowledge: research projects, journal submissions, collaborating institutions, regulating institutions.</td>
</tr>
<tr><td colspan="5">Feedback Mechanisms:
Electronic medical records, performance metrics, internal communications, patient/visitor satisfaction surveys, supplier communications, recognition/awards, employee reviews</td></tr>
</table>

Appendix 2

Table 5. Key Variance and Control Matrix.

Key Variances	Impact on Spread of disease	Who/Role	Observed when	How/Standard	Variance	Controls	Proposed Controls	Role
1. Perform hand hygiene	High	Entire hospital personnel	Before being in contact with a patient	Hand sanitizer: no isolation precautions	No use, improper use	No control	Sensitivity analysis on multiple controls	Entire hospital personnel
			After being in contact with a patient	Hand washing: isolation precautions	No use, improper use	No control	Compliance, effectiveness, different types of soaps	
				Improved hand washing: NICU		Timer		
				Surgical Scrub: before surgeries		Detailed scrub procedure		
				Gloves: isolation precautions, after surgical scrub	No use, improper use	No control		
2. Follow isolation precautions	High	Entire hospital personnel	When patient is placed in isolation	Contact Transmission: Hand washing, gown, gloves	No use, improper use	Other HCW	Sensitivity analysis on multiple controls	Entire hospital personnel
				Droplet Transmission: Hand washing, gown, gloves, masks, goggles	No use, improper use	Other HCW	Higher level of isolation, compliance	
				Airborne Transmission: negative pressure room		Airlock		
				Communication: sign, sticker, computer entry	No use, improper use	Other HCW		
3. Contacts with other HCWs	Moderate to high	Nurses	During meetings, lunch, sitting at nurse station	Meetings performed at nurse station (daily meeting and report)	Large group together	No control	Change meeting areas for reports	Nurses
4. Desinfecting rooms	High	Environmental Services	Daily cleaning	All surfaces desinfected	No checklist, "memorized"	No control	Sensitivity analysis on multiple controls	Environmental Services
			Room turnover	Spills cleaned and desinfected	Time based	Report system	Multiple fomites	
			After spill	Isolation rooms use PPE			Multiple desinfectants	
				Different desinfectants depending on the type of patient				
5. Laboratory based alert system	High	Laboratory technicians, nurses	After stool sample taken	Perform TechLab Assay on stool sample	Time to collect	HCW based	Expedite depending on patient	Nurses
					Time to perform	Lab queue	Prioritize ID labs	Lab Technician
					Process time	Lab Protocol	Faster process time	Lab Technician, TechLab
					Return time	HCW based	Prioritize positive results	Lab Technician
6. HCW and Patient education	Moderate	HCW and patients	Before coming in contact with infected patient	CDC precautions	No taught, pamphlets given	Periodic checks		Infectious Disease Preventionists
			Periodic Infection Control Training			No control for patients or visitors		Infectious Disease Preventionists
7. Use of antibiotics	Moderate to high	Physicians	After diagnose for other illness	Narrow spectrum, used only for secific treatment and for specific time	Overuse, overprescription	Medical profession	Education intervention	Physicians
8. Surveillance of infectious diseases	Moderate	Infectious Disease Preventionists	Before, during, after outbreaks	Passive: evaluate data from information system	Cases may escape	No control	Use of g-control charts	Infectious Disease Preventionists
				Active: look at specific pathogen	Slow response	Outbreak based	Use of g-control charts	Infectious Disease Preventionists

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5. Manuscript 3: *Development of a highly-detailed, highly-resolved in-silico hospital population to simulate outbreaks of healthcare acquired infections*

Abstract

Objective:
We developed a highly detailed simulation of a regional 700-bed hospital to better understand interventions against healthcare acquired infections (HAIs).

Background:
The cost of treating an HAI has increased dramatically in an already resource-strained healthcare system. Analysts use highly detailed simulation to understand epidemics and pandemics. We used the same tools to develop a hospital infection model to better comprehend outbreaks in hospitals.

Methods:
We obtained a year of electronic medical records data from a regional level 1-trauma hospital. We developed an *in-silico* population creator that can reproduce multiple types of hospitals. For this study we created a population that includes patients, healthcare workers, visitors, and patient room surfaces. We developed a disease model for a highly pathogenic bacterium called *Clostridium difficile*. We evaluated interventions to reduce the infection on the population. Finally, we recommended actions for the hospital.

Results:
We developed a highly detailed *in-silico* population of over 19,000 patients, 1,900 healthcare workers, 44,000 hospital visitors, and 1,000 hospital rooms. We observed 16 million contacts between agents, and 27 million total activities. We conducted 100 iterations of 200 simulated days. The combination of high percentage compliance to hand washing, room cleaning, and isolation of infected patients proved to be the best intervention for reduction of infections producing only 15 HAIs.

Conclusion:
The use of highly detailed simulation offers a novel and unique technique that can assess a wide range of interventions and provide guidance to infection control professionals. Furthermore, the hospital population can be used to test different pathogens. The type of intervention and the number of contacts are predictors for the number of infections in the hospital.

Key words: Simulation, computational epidemiology, healthcare acquired infections

1. Introduction

Healthcare acquired infections (HAIs) are a significant risk to populations in the healthcare system. HAIs are infections that a person acquires during their stay at a hospital or a healthcare facility. In the United States, 1 in every 20 hospitalized patients becomes infected with an HAI, and twenty percent of HAI patients acquire their infection in an intensive care unit (ICU) (Centers for Disease Control and Prevention, 2012). In the United States, *Clostridium difficile* has replaced methicillin-resistant *Staphylococcus aureus* as the most prevalent healthcare-acquired pathogen and it is also the most common cause for healthcare associated diarrhea. *Clostridium difficile* is a normally occurring bacterium in a person's intestinal flora that can cause severe disease when perturbed by antibiotics (Karen & John, 2011). Risk factors include advanced age, underlying illness, and long length of stay in a hospital (Bignardi, 1998; Sunenshine & McDonald, 2006). In mild cases *Clostridium difficile* can cause diarrhea, however in severe cases this infection can be fatal. The rate of relapse for CDI is estimated to be between 15 and 35 percent (Lyerly, Krivan, & Wilkins, 1988; Sunenshine & McDonald, 2006).

Transmission of this pathogen occurs through the spread of spores released from an infected patient. These spores can spread through the hospital via direct contact or through infected surfaces. The best prevention measures include adherence to hand hygiene, isolation precautions, and appropriate room cleaning. Other methods that have been used for prevention include extended disinfection, visitor guides, and checklists (Abbett et al., 2009; Whitaker, Brown, Vidal, & Calcaterra, 2007). Medical therapy for *Clostridium difficile* infection includes antibiotics such as Flagyl, Vancomycin, Bacitracin (Tomkins, Raynor, Rothwell, DeSilva, & Wilson, 2011; Yoo & Lightner, 2010), and just recently Fidaxomicin (Babakhani, Gomez, Robert, & Sears, 2011; Linsky, Gupta, & Hermos, 2011; Louie et al., 2011; Tannock et al., 2010). Other treatments such as a vaccine and fecal microbiota transplantation have been studied with high success in small groups (83% to 100% for FMT), but are not currently recommended or readily available for therapy (Aboudola et al., 2003; Brandt & Reddy, 2011; Gardiner, Rosenberg, Zaharatos, Franco, & Ho, 2009; Karadsheh & Sule, 2013; Kelly, de Leon, & Jasutkar, 2012; Kyne & Kelly, 1998; Lyerly et al., 1988; Oberli et al., 2011; Yoo & Lightner, 2010).

In most hospitals, prevention measures and medical therapy are applied in a combined fashion (bundle) to maximize the effectiveness of treatment against a pathogen. However, it is very difficult to determine the effectiveness of individual interventions or of different types of bundles. Furthermore, testing multiple interventions could prove to be infeasible, impractical, or unethical in certain cases. Simulation of healthcare systems can help bridge the gap between developing new interventions and the inability to test them in hospital environments.

Health systems simulation is the utilization of computer simulation techniques to improve the performance of healthcare facilities. The concept of healthcare facility simulation is not new and many different methods have been utilized to analyze patient safety, quality of healthcare, and efficiency (Brailsford, Harper, Patel, & Pitt, 2009; Fone et al., 2003; Keeling & Rohani, 2008). Most of the methods utilized in the past are effective in demonstrating the general behavior of the population, but they do not have the ability to demonstrate individual behaviors. The focus of our study is to develop a bottom-up, individual behavior based model. We developed a high-detail, high-resolution, synthetic (computer generated) population of a level 1-trauma hospital to determine the factors that can help reduce the spread of *Clostridium difficile*. For this purpose, we utilized EpiSimdemics, a scalable parallel computing algorithm capable of computing epidemics over large social contact networks (hundreds of millions of individuals) (C. L. Barrett, Bisset, Eubank, Feng, & Marathe, 2008).

2. Methods

We developed a hospital population following the principles of highly-detailed simulation: develop an in-silico population (or proto-population), develop a disease model for a specific pathogen, develop interventions, and conduct simulation and analysis (C. Barrett et al., 2009). The methodology phases and steps are presented below in figure 1. Phase 1 consisted of the collection of data and development of a synthetic or *in-silico* hospital population. A synthetic population is a digital representation of people. Synthetic populations are not exact representations of the real human population, but they approximate their actions and demographics to a very high degree of detail. Utilizing this type of population allows researchers to introduce interventions that could not otherwise be tested on real subjects. In addition to the population, this phase included the construction of activities of every agent in the population. Phase 2 consisted of developing a disease model of *Clostridium difficile*. A disease model is a representation of a disease or infection based on the different health states that a person goes through. Phase 3 consisted of the development of sociotechnical interventions for the simulation. Depending on the type of intervention, the programmer modifies either the synthetic population and activity files or codes the intervention directly into the main simulation program. Finally, phase 4 consisted of running the simulation and analyzing the results with multiple software packages.

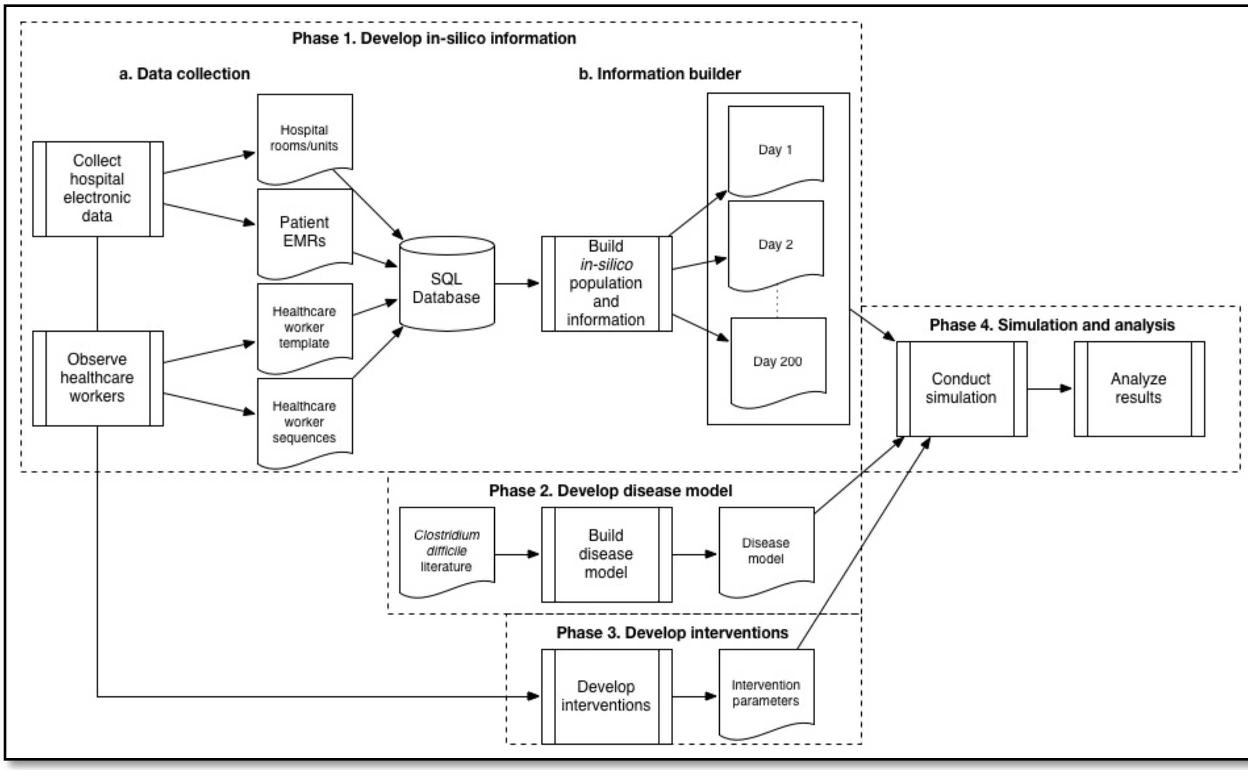

Figure 14 (Figure 1, Manuscript 3): Methodology to develop a hospital simulation

Phase 1: Development of in-silico information

a. Data collection

We collected hospital data from electronic medical records at a level 1-trauma hospital in Virginia. This data covered a year of patient admissions. In order to protect patient privacy, the records did not have any identifiable characteristics to link back to the patients. The records included information on length of stay, patients' room and hospital unit, procedures performed, and demographic characteristics of the patients. Additionally, we conducted direct observations of healthcare workers in over 30 different medical disciplines. The author shadowed a representative of each hospital discipline from 4 to 8 hours during regular work shifts and recorded information regarding activities, locations, and contacts with other people within the hospital. The author protected the identity of the study subjects by de-identifying field notes. Additional population details included high contact surfaces in the patients' rooms (beds, chairs, computers, monitors) and hospital visitors. The data gathered at the hospital was entered into a secured Structure Query Language (SQL) database for privacy protection. The Virginia Tech Office of Sponsored Projects and the Carilion Clinic IRB approved an Institutional Review Board (IRB) request for this project.

b. Development of the information builder software

The data obtained from the data-gathering step was the main input for the next step: information-builder software. We developed a modular, information builder program that is able to create synthetic hospital populations through the use of multiple "flat" file data inputs. Figure 2 below shows the system representation for the information builder. The program is initialized with five input files. The patient file includes data on patient locations, activities, times, and patient number (the patient number cannot be used to identify actual patients). The patient rooms file includes all the patient room numbers in the hospital as well as the hospital unit, and unit numeric code (assigned during the construction of the data file). The healthcare worker file is a template that specifies the type and number of healthcare workers required at each unit in the hospital. The healthcare worker activity list was derived from direct observations and it incudes the type of activities that each healthcare worker can perform. Each type of healthcare worker has a separate list of tasks, durations, and locations for these tasks. Additionally, each healthcare worker task was assigned either a high, normal and low duration for each activity from their particular list. The next module in the program has a function that randomly choses one of the three durations for the activity. This feature ensures that not all healthcare workers are conducting the same activities and that the duration of their activities is different per person. Finally, the healthcare worker rooms file contains all the rooms that are used exclusively by healthcare workers such as lounges, locker rooms, nurse stations, and janitor closets. Any of these files can be modified to change the population, activities, or locations. All of these information files are placed in an SQL database.

The next step in the builder program is to create activity files for each individual agent in the simulation. The program can search through the input files and assign tasks, durations, and locations of these tasks. The activities for each healthcare worker are aggregated at the unit and later at hospital level. The final list includes healthcare worker identification number, hospital unit, activity type, location, and duration of the activity. The list feeds the daily schedule creator module.

The visitors and room surfaces lists are developed using the original patient list as a template. Each patient has the same number of room surfaces in their room, but they can be assigned a varying number of visitors. The number of visitors is randomly defined by a probability function in the person builder module. The next step in the process is the activity builder module. This module creates individual activities for each patient, visitor, and room surface. For the purposes of this study, room surfaces remained in the same location. If necessary, it is possible to program motions of objects such as computers or monitors. Finally, the activities of each patient, visitor, and room surface are aggregated into a hospital unit based file. The file includes identification number, location, sublocation, hospital unit, type of activity, and duration of the activity. The final step in the builder program is to create daily schedules for each individual agent in the simulation. These schedules include location, sub location, type of activity, and duration of the activity. The output files are the input for the EpiSimdemics algorithm. For this study we chose to replicate the patient, healthcare worker, and visitor activities for a period of 200 days.

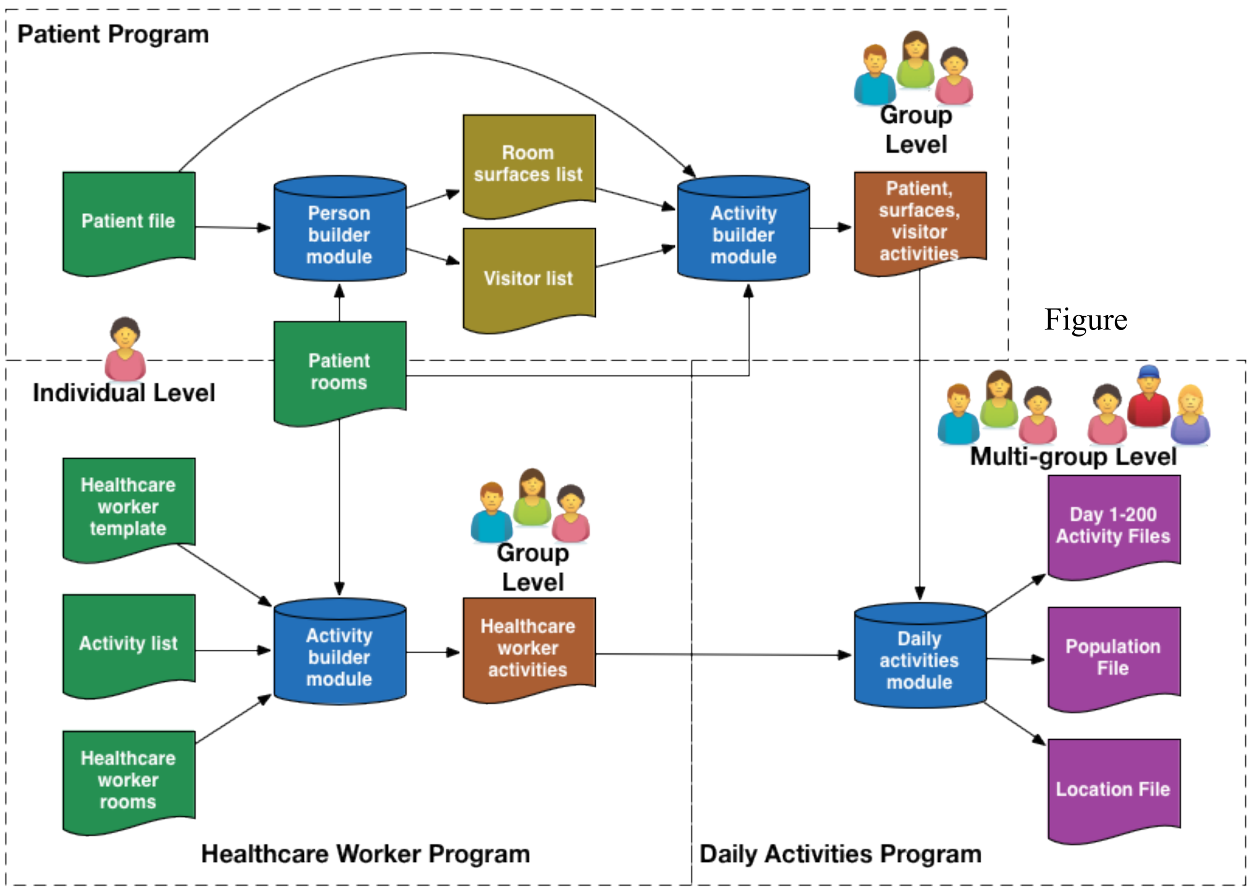

Figure 15. (Figure 2, Manuscript 3). Builder program system schematic.

One important portion of the simulation is the development of activities that occur in each patient room. The patient rooms were designed based on the layout of current hospital rooms. Each bedroom was divided into 5 different sublocations. Each sublocation has surfaces that can be contaminated and/or cleaned by environmental services personnel. The movements of patients, visitors and healthcare workers were also programmed based on the layout of the patient room. Motions of each agent were developed from direct observations that were later developed into general rules for types of agents of the same kind. For example, healthcare workers were programmed to enter the room, wash their hands, interact with the patient, interact with different surfaces, and finally move on to their next patient. Each type of healthcare worker conducts different activities with different durations. Every activity was programmed with a triangular distribution for its duration (short, normal, and high duration) as explained before.

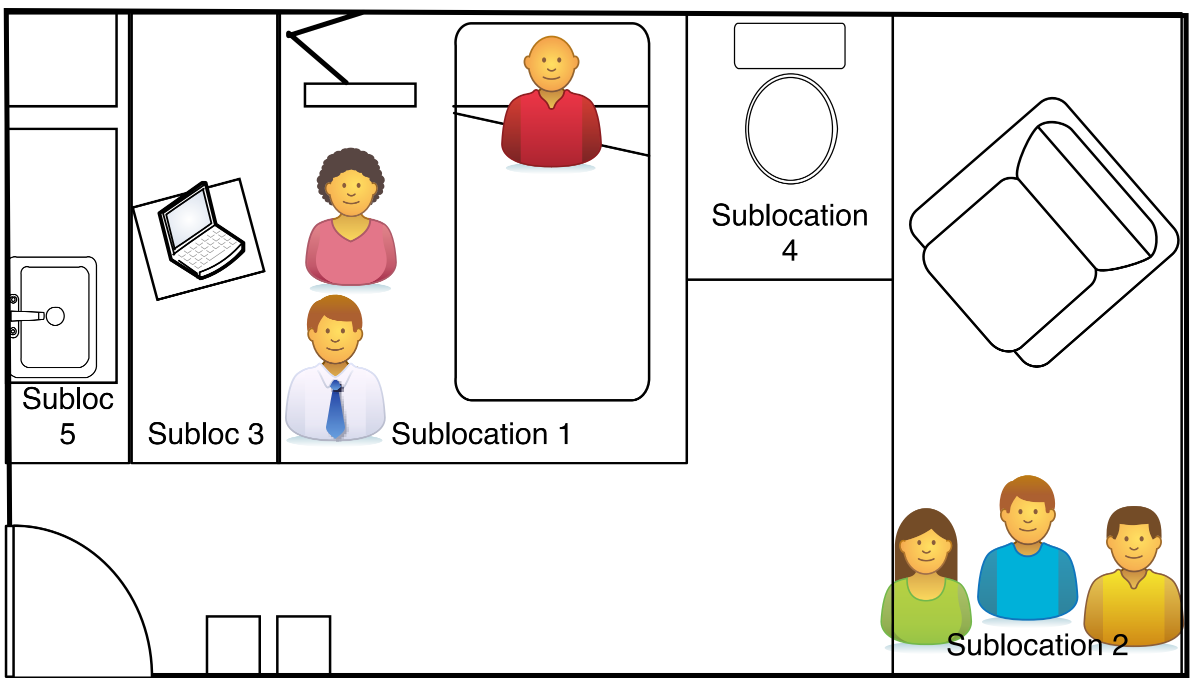

Figure 16 (Figure 3, Manuscript 3). Example of a patient room layout as it was programmed for the synthetic population builder.

Healthcare workers conduct daily activities around the patient. Visitors have contact with the patient and stay in the visitor section of the room. Room surfaces have been added to the model in multiple sublocations, and can become contaminated by and/or contaminate other agents.

The social network is the main contact structure for the population. It represents the framework on which the infection and subsequent interventions will flow through the population. EpiSimdemics utilizes the information created during Phase 1 and applies the disease model and interventions to every synthetic agent. The process in which the EpiSimdemics algorithm creates a social contact network and performs simulations of outbreaks has been documented extensively (C. Barrett, Bisset, Leidig, Marathe, & Marathe, 2010; C. L. Barrett et al., 2008). Additionally, multiple studies have been completed in large populations with multiple scenarios (Lewis, 2011) to include a simulation with an in-silico representation of every individual in the United States, including their household structure (C. Barrett et al., 2009).

Phase 2: Development of the disease model

The next phase in this methodology involves the development of a disease model for the simulation. We developed a disease model based on the most current literature for *Clostridium difficile* infections (Carrico et al., 2013; Cohen et al., 2010; Karadsheh & Sule, 2013; Sunenshine & McDonald, 2006). The disease model includes the different health states that any agent in the population may be in at any time during the infection. Figure 3 was used in a prior paper, but also applies to the disease model utilized in this study. This figure shows the disease model and the multiple health states developed for this simulation. Each agent will start at the uninfected state. This state has different susceptibilities to infection depending on their age. Each health state has different transitions based on probability. These transitions are either preventive measures or pharmaceutical therapies typically used in the treatment of CDI. In the simulation, the disease model acts as a finite state machine in which each transition has different probabilities that allow each agent to progress through the disease model.

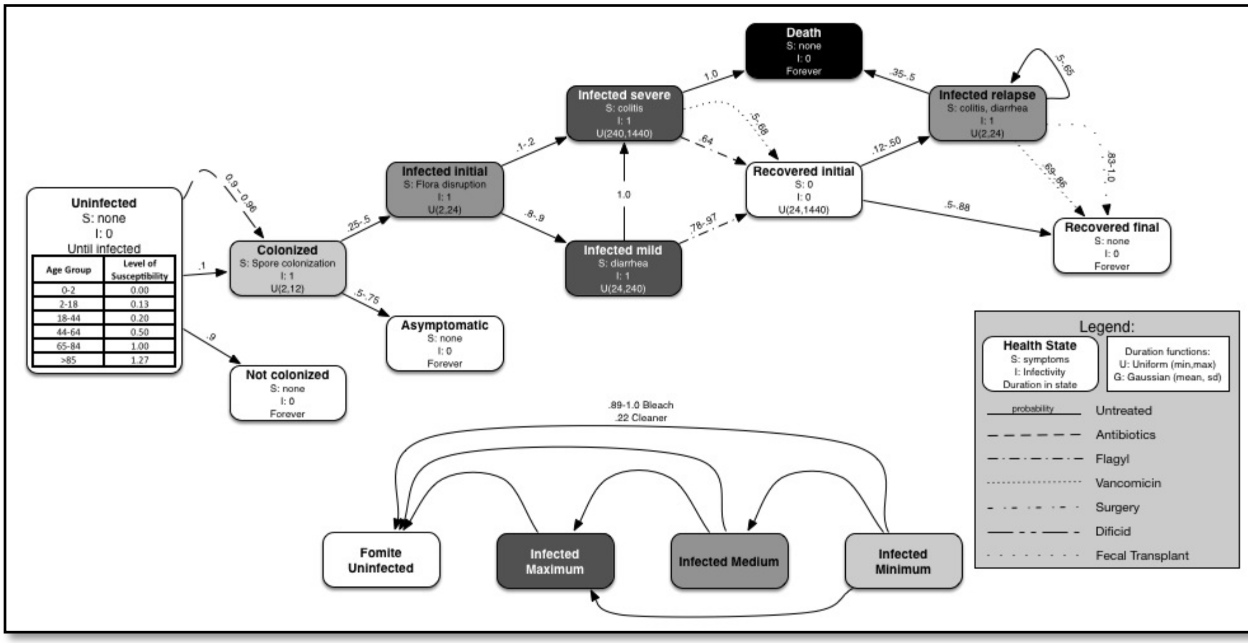

Figure 17 (Figure 3, Manuscript 3): ***Clostridium difficile*** **disease model and parameters**

(Jimenez et al., 2014)

Phase 3: Development and evaluation of interventions

The interventions utilized in this study were chosen from current medical treatment for patients with CDI. The most common prevention interventions are thorough hand washing by healthcare workers, room cleaning with quaternary disinfectant and bleach, and isolation of infected patients. As mentioned in the introduction, there are also recommended medical treatments. However, we focused our study towards sociotechnical interventions that did not include changes in medical treatment. Our study does include the medical treatments in the disease model parameterized according to the literature.

a. Intervention sensitivity analysis

As a method to screen interventions, we prepared sensitivity analysis on three different major interventions: hand washing, room cleaning, and patient isolation.

Hand washing:

Healthcare workers were programmed to use the faucet in the patient room whenever they exited or entered a patient room. The faucet was programmed to completely clean the healthcare worker from any contamination that he or she may have acquired from the patient, visitors, or room surfaces. The sensitivity analysis was achieved by varying the percentage of decontamination that the faucet provides for each healthcare worker. This action, in fact simulates whether or not healthcare workers are washing their hands in the proper manner.

Room cleaning:

Room cleaning involved programming environmental services staff and the room surfaces to interact by proximity of each other for surface decontamination. Environmental services agents were programmed in the simulation to visit a limited number of rooms during their daily duties for cleaning and decontamination. Each environmental services agent visits different locations within the patient rooms to ensure that all surfaces are cleaned. As explained before, we created a limited number of room surfaces to simulate. However, in the future, additional surfaces could be created all over the hospital. The sensitivity analysis for this intervention was achieved by varying the percentage of cleaning and decontamination from the environmental services staff for each surface. By conducting this action, we simulated whether or not a surface is being cleaned properly.

Community-acquired infection patient Isolation:

The isolation intervention was accomplished by selecting actual community-acquired cases. This information was obtained from the electronic medical records (Phase

1a). These patients are place in a special health state within the disease model. No other agents can be contaminated through contact with the isolated patients. The diagnosis of CDI is fairly rapid, so for the purposes of the simulation, we placed the community-acquired cases in isolation the following day of their diagnosis.

b. Combinations of Interventions

We conducted experiments utilizing combinations of interventions to determine the best type of intervention to apply for the hospital. Design of Experiments (DOE) has been utilized for a long time in statistics. We used a DOE model from SAS JMP Pro 10 statistical software. The table below shows the experiment runs and the combinations of each factor (intervention). The results were also analyzed utilizing SAS JMP Pro 10 software.

Table 6 (Table 1, Manuscript 3). Factor combinations for experiments.

Intervention 1	Intervention 2	Intervention 3	Infection Cases
Hand washing 50%	Room Cleaning 50%	Isolation	104.21
Hand washing 50%	Room Cleaning 95%	Isolation	88.52
Hand washing 50%	Room Cleaning 50%	No isolation	106.8
Hand washing 50%	Room Cleaning 95%	No isolation	90.49
Hand washing 90%	Room Cleaning 50%	Isolation	42.35
Hand washing 90%	Room Cleaning 95%	Isolation	41.28
Hand washing 90%	Room Cleaning 50%	No isolation	43.62
Hand washing 90%	Room Cleaning 95%	No isolation	42.54

Phase 4: Simulation and analysis

This study simulated the contacts of the entire hospital population for a period of 200 days. The study contained over 19,000 patients, 1,900 healthcare workers, 44,000 hospital visitors, and 1,000 hospital rooms. We observed 16 million contacts between agents and over 27 million total activities. Each 200-day simulation was iterated 100 times for each scenario.

We included some assumptions and simplifications in the simulation model due to lack of data available and the large size of the current population. Prior existing medical conditions of the agents, other than age or use of antibiotics, was not a factor in the disease model. Co-morbidities were also not taken into account in the disease model. The study is limited to infection on the hospital's grounds except for those patients who had been identified as having community-acquired infections. Once any of the agents left the premises of the hospital, the infection could not affect them.

3. Results

We observed over 16 million contacts between the different types of agents in the simulation. We classified contacts as two or more agents conducting an activity at the same time in the same location and sublocation. Based on the disease model, an agent who is in contact with another agent has the possibility to initially infect him. As explained before, each patient room was programmed with five different sublocations (bed, visitor, faucet, toilet, and computer areas). Contacts can also occur between different types of agents, therefore a patient can have direct contact with the bed or a visitor can have direct contact with a visitor chair. Figure 4 shows the hospital as a sociogram, a representation of all the contacts (lines or edges) between all the different types of agents (spheres or nodes).

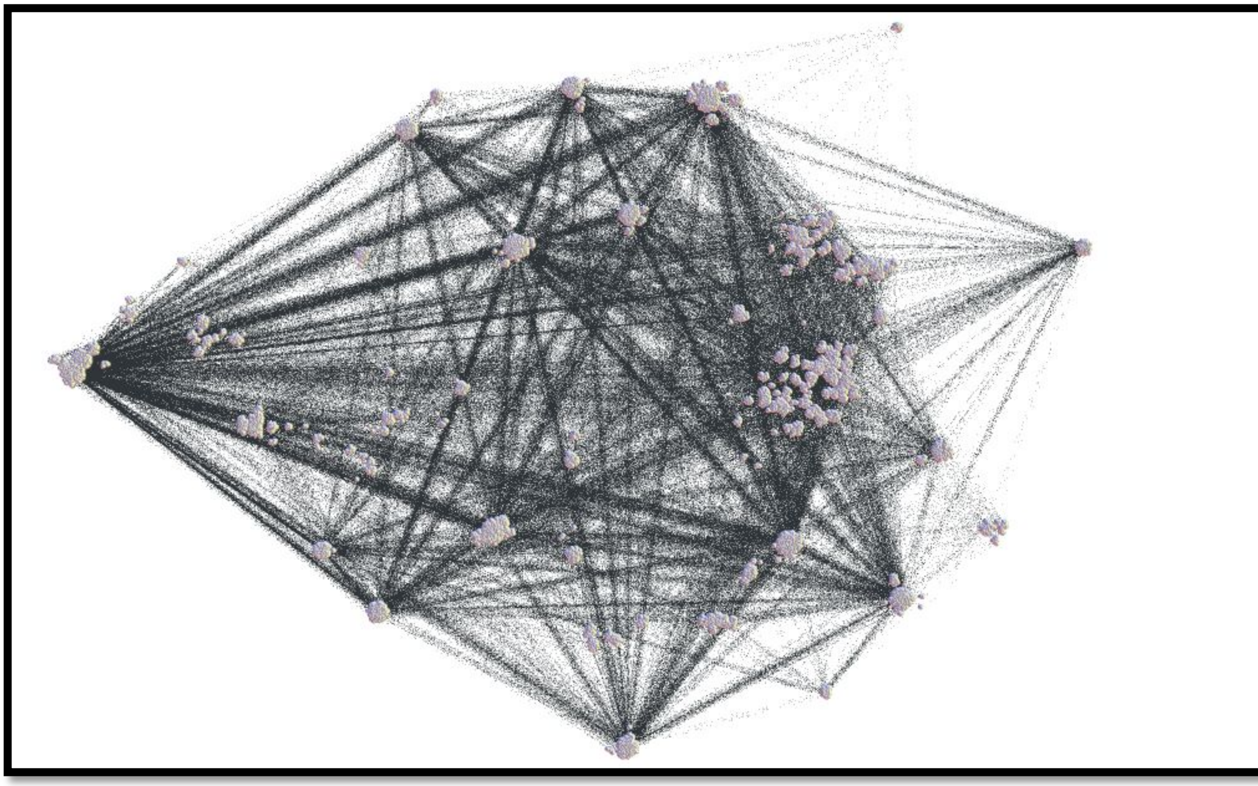

Figure 18 (Figure 4, Manuscript 3). Sociogram of the hospital. Every agent and contact are depicted in the diagram.

We initially conducted sensitivity analyses on the three interventions as screening experiments to determine high and low levels. The hand washing intervention had the highest sensitivity to changes varying from 39 to 270 cases. Figure 5 shows the cumulative case count for multiple levels of hand washing compliance. Based on this screening experiment, we chose 90% compliance as the high level and 50% compliance for the low level. Following the same approach, we chose 95% effectiveness in room cleaning as the high level and 50% as the low level. Sensitivity on room cleaning was not as high as hand washing, but the difference between levels was statistically significant.

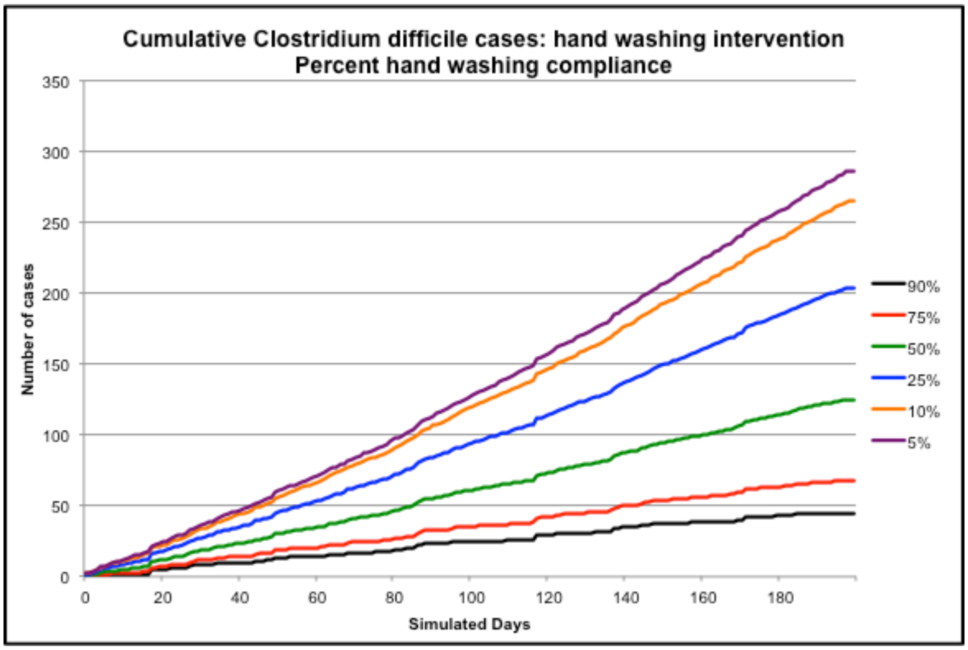

Figure 19 (Figure 5, Manuscript 3). Sensitivity analysis of hand washing intervention. Each line represents a different level of compliance from healthcare workers.

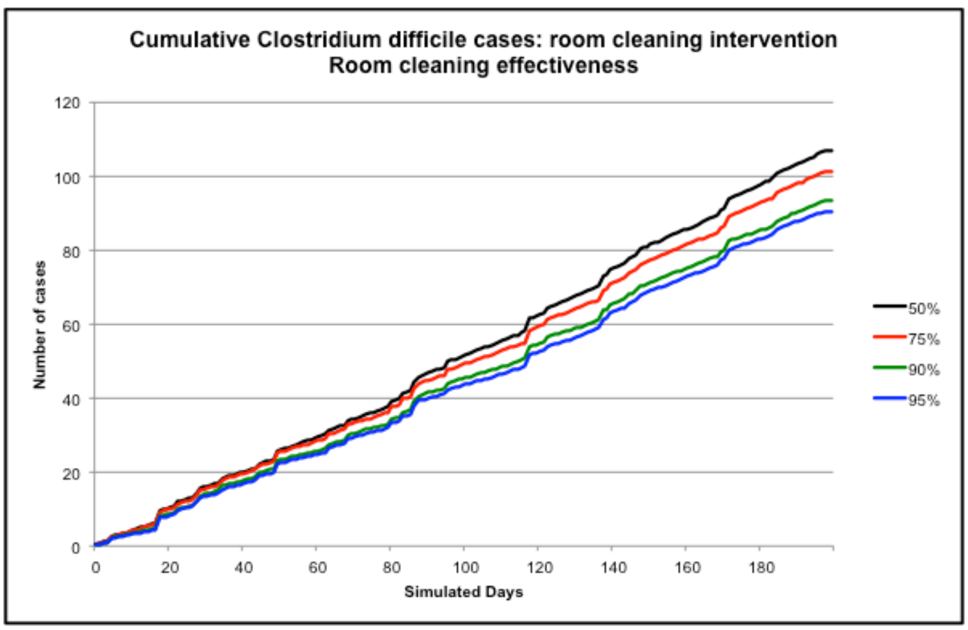

Figure 20 (Figure 6, Manuscript 3). Sensitivity analysis of room cleaning intervention. Each line represents a different level of cleaning effectiveness.

Figure 7 shows the results obtained for each of the intervention combinations. The lowest rate of infection was obtained by combining a high compliance in hand washing

(90%), high level of effectiveness on room cleaning (95%) and isolation of community-acquired cases. Significant reductions were also achieved at different levels of hand washing and room cleaning. Figure 8 shows the prediction profiler function for Design of Experiments in SAS JMP Pro 10. The profiler provides a feature in which combinations of interventions (statistical treatments and levels) can be modified to achieve an optimal solution. Furthermore, DOE designs allow researchers to determine interventions and levels of interventions to obtain a specific result (in our case cumulative infections).

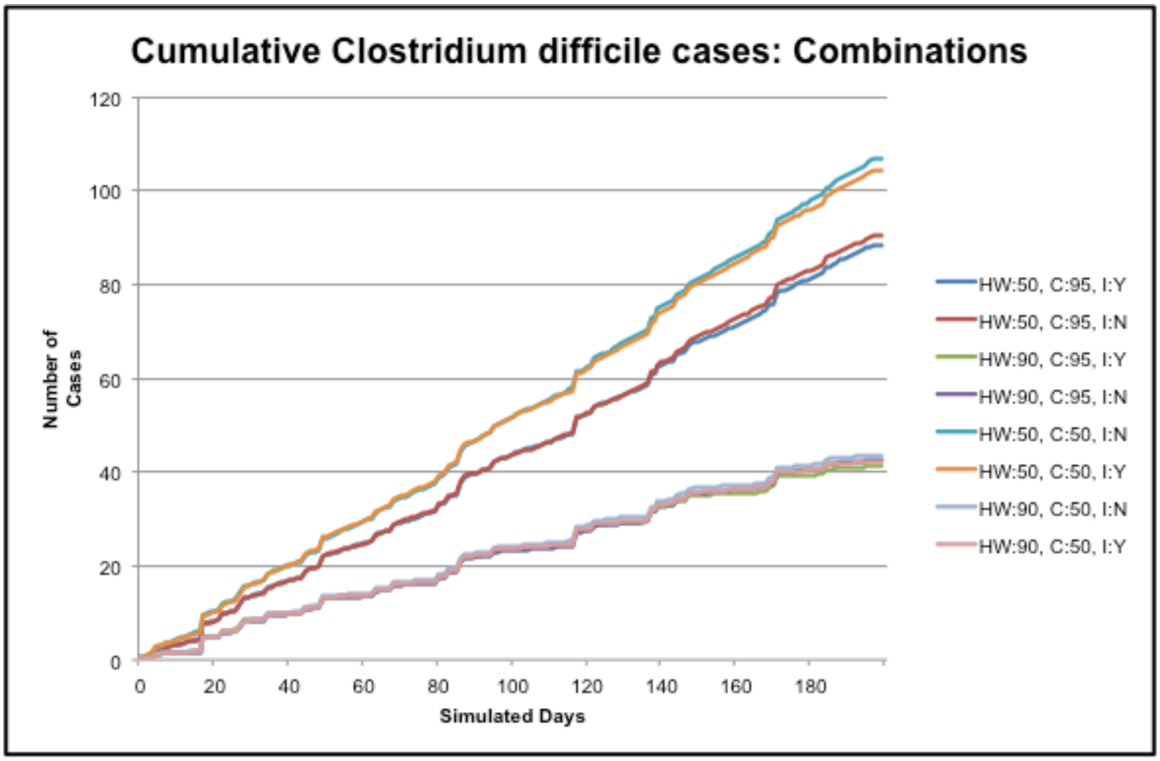

Figure 21 (Figure 7, Manuscript 3). Design of experiment results for combination of interventions.

Factors were coded as hand washing at 50% (HW:50), hand washing at 90% (HW:90), room cleaning at 95% (C:95), room cleaning at 50% (C:50), isolation (I:Y), no isolation (I:N).

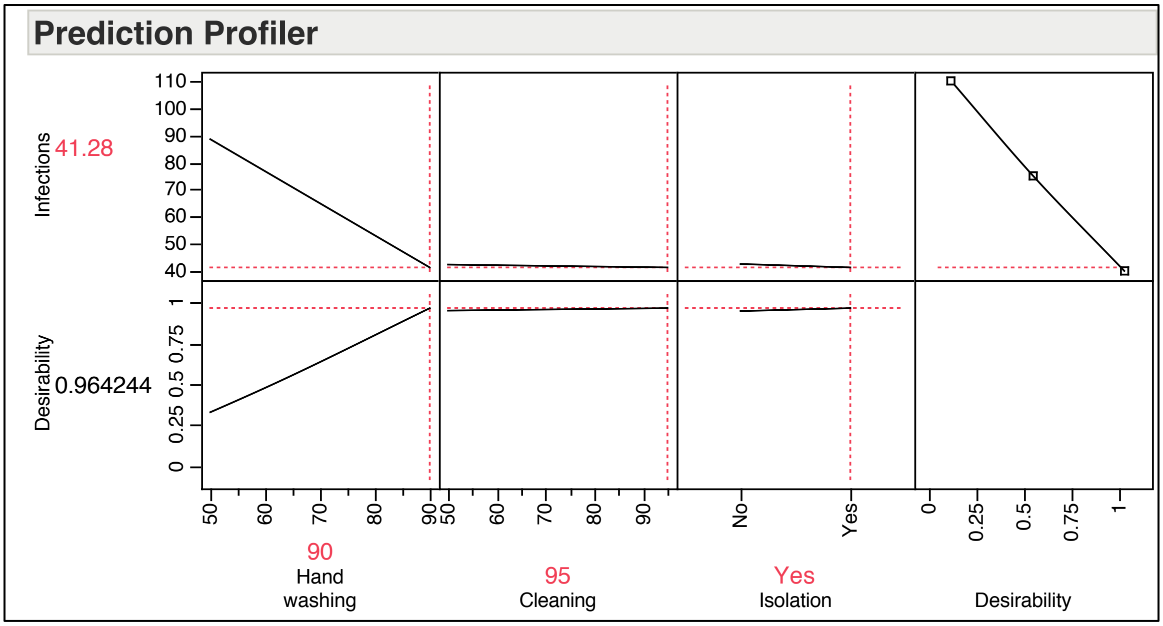

Figure 22 (Figure 8, Manuscript 3). Results of the design of experiments.

4. Discussion

One of the major strengths of this study is that patient and healthcare worker data was obtained directly from the hospitals through chart review and observations. This ensures that the population builder has a very high level of detail and resolution when it comes to individual actions. The activities derived through the population builder include daily activities for all agents, meetings, rest breaks, and lunch breaks for healthcare workers, and even visitors and patients leaving the hospital to go back their homes. Furthermore, the population builder is modular, meaning that it can be adapted to multiple types of hospitals (scalable). The activities and simulation were additionally calibrated for all it parameters with actual community acquired cases that occurred in the hospital. During the 200-day period that we chose to observe, we detected 26 community-acquired cases and 115 hospital-acquired cases. This information allowed us to calibrate the parameters as close as possible to the real infection. Another important aspect to remember about simulation is that no matter how detailed, a simulation can never be exact. There are too many variables that can affect the results. With the help of probability, we can develop simulations that can account for many of those variables. However, a simulation will only provide the level of detail that it has been programmed to represent.

The hand washing intervention proved to be more effective in reducing CDI than other interventions. It is important to mention that along with the hand washing intervention, we programmed all healthcare workers to be able to wash their hands, which can become dirty as they perform their daily tasks. Isolation appears to have less flexibility in reducing infections. However, isolation can help reduce infections if other interventions are followed appropriately. In other words, a person can be placed in isolation, but if the healthcare workers do not comply with hand washing or cleaning regulations, that person could be at the same risk as not having isolation restrictions. Although the best results were obtained by combining the best levels for each intervention, analysts should not ignore other results. A hospital might not have the ability to operate with high rates of effectiveness in room cleaning or hygiene precautions. However, with the help of simulations of this kind, stakeholders can make an informed decision on where to allocate resources.

For this simulation model we made certain assumptions to aid in reducing the complexity of the environment we were recreating. First, we made the assumption that compliance with prevention measures such as hand washing, room cleaning, or isolation. Secondly, we did not take into consideration multiple diseases. This extension of the study is possible to complete, but requires a large amount of computer memory. We utilized the principle of multiple finite state machines in a disease model in order to represent the room surfaces contamination. It is important to note that this model created data results of 10 megabytes per simulation iteration. Additional finite state machines could create larger files. Finally, we conducted our study for the period of 200 days. This period of time may not be enough time to observe the full effect of the disease model on agents. In the future, we plan to conduct studies that observe a period of time of 400 days or more. This will add additional detail to the model and allow for more complex interactions between agents.

It should be no surprise to healthcare workers or infection preventionists that the best outcomes occur with high levels of effectiveness and compliance to infection preventions. Hand washing, room cleaning, and isolation are the main interventions utilized in hospitals to avoid spread of infection. Furthermore, there are multiple studies that utilize these interventions at different levels to study the infection rates at clinics and ICUs. What is new with this study, is the ability to study multiple, tailored interventions applied to the entire hospital population. Most studies, due to limitations in computer power and the complexity of hospital data cannot provide this level of detail and resolution. Another aspect that is not too evident is the ability to provide healthcare stakeholders with different levels of intervention combinations. These combinations can be used to make important decisions on resource allocation.

Future Work

For our future work, we will continue to evaluate different types of interventions through the use of this hospital model, combining multiple disease models. Our goal is to approximate our model to the complexities of hospital operations. Furthermore, we have developed two more hospital models utilizing the same methodology. The first model and its respective research article discuss the use of macroergonomics or systems ergonomics as a framework in developing sociotechnical interventions (Jimenez et al., 2014). We evaluate those sociotechnical interventions through the use of the EpiSimdemics algorithm. The second model is a representation of a Combat Support Hospital. This model will evaluate the spread of infections in the different levels of military healthcare (medic to theater hospital) following battlefield wounds.

5. Conclusion

This work represents the first steps towards a truly comprehensive hospital simulation that one day may included every single surface, person, and activity for any type of hospital. We developed a hospital simulation following 5 distinct phases. For our first phase we collected data from a 700+ bed hospital and we developed an *in-silico* or synthetic population through a population builder based on Python computer language. In phase 2 we developed a disease model based on *Clostridium difficile* literature. This model also included contamination of room surfaces. During phase 3, we chose 3 interventions to evaluate with the EpiSimdemics algorithm. Finally, we conducted a Design of Experiments with a combination of factors and levels of the three interventions. In prior works we have included other interventions. However, for phase 4, we wanted to dive deeper into the main existing interventions that hospitals currently use. In the future we expect to simulate different medical treatments and longer periods of time. We believe that this methodology can assist in determining appropriate interventions against healthcare acquired infections.

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6. General Conclusions

Throughout this work I have learned that utilizing a multidisciplinary approach can be a powerful tool to identifying and analyze interventions to reduce healthcare acquired infections. Highly detailed simulation and macroergonomics can complement each other for the analysis of HAIs and other pathogens. By utilizing simulation, an analyst can evaluate multiple interventions in a flexible environment. Some times these interventions could be difficult, expensive, or even unethical to test. Simulation provides a safe environment to effectively and efficiently provide analysis to stakeholders. The macroergonomics worldview allows an ergonomist to understand the world through the systems perspective. He can develop interventions that look at not only changing technology alone, but also aim to understand the entire production or service process together. Systemic interventions, especially once that encompass the entire work system, can be very useful in the fight against HAIs.

Healthcare workers are at risk of becoming contaminated or infected with healthcare acquired infections. One of the aspects that protect them is the ability to engage in guided precaution measures. During our study we saw very limited exposure and contamination by healthcare workers. The systemic interventions that were applied to the entire synthetic population might have had a significant role in this result. Appropriate precautions should be taken by the entire personnel subsystem in a hospital to reduce exposure.

There are multiple reasons why infection rates could be increasing in healthcare facilities. The main reason that we studied in our research was the lack of compliance to rules and guidelines for infection control measures. However, it is possible that not only the lack of compliance may be causing the increase, but also the cultural predisposition of healthcare workers in a hospital. We can assume that most prevention guidelines have been put in place in hospital because they were successful in pilot studies, or because the literature supported their use. However, there comes a point that adding more rules governing infection control can have a detrimental effect on the operations of the hospital. It is possible, additionally, that the culture that exists inside the hospital, the community, and even in our country could be having a negative effect on our efforts to reduce HAIs. What if the reason for the lack of control had to do with a culture in healthcare facilities in this country in which completing tasks on time, turning over a bedroom, or preparing equipment for the next patient is more important that infection control precautions? What type of precautions could then be put in place to reduce the spread of disease at the cultural level? Conducting research on how culture directly affects the outcome of HAIs could be a very interesting research study for future work.

Future work in this field should also look at conducting more highly detailed simulation simulations for hospital environments. There are still many research questions to be answer and this work represents just the surfaces of what our team can accomplish. We are expecting to introduce more hospital surfaces into the simulation; as well as more macroergonomics based sociotechnical interventions and combinations of those interventions. We would also like to add additional disease models, and test new technology such as Xenex® and other cleaning machines. We have also developed a model for a combat support hospital (CSH) that is ready for use and for intervention testing.

To conclude, I have learned that *Clostridium difficile infection,* just like other healthcare acquired infections, is very rare. The infection rate in hospitals in the United States is about 7 per 10,000 patient days. However the suffering to families, work places, and the cost to society should motivate us to find effective solutions to this problem. In the end, the work that healthcare workers such as physicians and nurses perform focuses on one objective: saving human lives. As researchers in this field our objective should be to help them in this endeavor.

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