Investigating the Historical and Social Reasons Behind the Stagnation and Failures in *Clostridioides difficile* Infection Treatments

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science
University of Virginia, Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science, School of Engineering

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Spring 2024

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

Clostridioides difficile (*C. diff*) is an infectious bacterium contracted in healthcare-related settings at a high rate, causing colitis and diarrhea which can be severe and life-threatening. *C. diff* infection (CDI) is the primary cause of antibiotic-associated and infectious diarrhea in hospitals (Viswanathan et al., 2010). It has an estimated prevalence of 500,000 cases annually, and growing incidence and mortality rates (Guh et al., 2020). High-risk conditions for this infection include prolonged hospital stays, weakened immune system, and, notably, recent antimicrobial therapy and older age. In most cases, healthy gut bacteria prevent *C. diff* from colonizing, but when broad-spectrum antibiotics are used to treat other health conditions, the normal gut microbiome is disrupted, increasing susceptibility to *C. diff* infection (CDC, 2022). Those who contract *C. diff* face gastrointestinal symptoms, particularly diarrhea, stomach pain, and fever. In addition to its large healthcare burden and severity, CDI poses a unique problem due to its cyclical nature; it has high recurrence rates. Around 1 in 6 CDI patients will contract it again in the 2-8 weeks following recovery. Typical treatments for CDI involve narrow-spectrum antibiotics, which continue to disrupt healthy gut bacteria, making recovery more difficult and contributing to high relapse rates (Goudarzi et al., 2014).

Recently, fecal microbiota transplants (FMT), an alternative therapeutic for treating recurrent CDI have had high success rates, as they introduce a healthy community of microbes to the colon to help restabilize the microbiota. This technique involves processing donor stool for the healthy microbial community within it, and transplanting that into a patient so that the healthy microbes may recolonize the gastrointestinal tract. (Wang et al., 2019). However, this can be expensive, inaccessible, and unappealing to patients. Due to these factors, there is a large need

for a more accessible and affordable treatment for recurrent CDI that can restore healthy microbiota by re-establishing natural colonization resistance.

Medical therapeutics have advanced greatly over the last few decades due to the innovation in research and technology that has been integrated with the biomedical field. In fact, the number of new drugs approved each year by the FDA is 60% greater than the yearly average in the previous decade (Congressional Budget Office, 2021). Yet, many patients receive the same antibiotics for CDI as the ones that were given 50 years ago (Bartlett, 2008), which raises the question of why this field of disease has seemingly been left behind in the expanse of medical turnover that has been facilitated by technology. Despite attempts at alternative therapies, such as FMT, new therapeutics have not been implemented in a widespread, systematic manner.

This paper explores the historical timeline of CDI, from the discovery of the *Clostridium difficile* bacterium, through the variety of research in therapies that has been conducted to answer the question of why there has been a stagnation in treatment for CDI. Additionally, I provide an overview of the social aspect of this disease, such as public perceptions and media framing of CDI, as well as public perception of alternative therapies. Through my literature review, I cover the development and discovery of the primary antimicrobial therapeutics still in use today, as well as how historical barriers in the healthcare industry and clinical inertia can contribute to stagnation in research. I provide an overview of the diagnostic techniques used for CDI and analyze how systemic complications in this process have downstream effects. In this paper, I argue that the combination of lack of education, inaccessibility to treatment, clinical barriers, and patient fear have worked in conjunction to impede research as well as the deployment of effective, innovative therapeutics by using a historical analysis through the lens of Diffusion of Innovation. Through my analysis, I intend to uncover a relationship between socio-technical

aspects, such as media literacy and public perception, and the stagnation in innovation for CDI treatment.

Literature Review

Originally, *Clostridium difficile*, an anaerobic bacterium, was identified as a part of the gut flora of healthy infants in 1935 (Smits et al., 2016). Three separate lines of work later converged to foster initial knowledge of CDI: preliminary studies on the microbe, investigation of typhlitis in rodents, and studies of pseudomembranous colitis (PMC). In the initial studies of *C. diff,* it was noted by researchers that it could be a source of disease in animals due to the production of a secreted toxin that was highly lethal to mice but was shown to be biologically unimportant. In 1893, J.M.T. Finney, who performed the first anatomic studies of PMC, reported pseudomembranous changes in the intestinal tract of a patient, and PMC became a commonly recognized complication following antibiotic use (Bartlett, 2008). Before 1978, a large library of information had been discovered about both PMC and CDI, but the two were yet to be linked. Around this time, a rapid amount of research was produced that led to the eventual identification of *C. difficile* and its toxins as the cause of clindamycin-associated colitis. For example, it was understood that the cytopathic effect of the stools of PMC patients was due to toxigenic clostridia, a pathogenic class of bacteria (Gerding, 2009). Even before this influx of information, an antibiotic called vancomycin was discovered as one of the earliest and most effective treatments for CDI, in the 1950s (Bartlett, 2008). Today, the first and most common treatment is still antibiotics, such as metronidazole, vancomycin, and fidaxomicin (O'Horo et al, 2013).

In addition to antibiotics, alternative therapies for CDI have recently been introduced with moderate success. One instance of this is the use of immunoglobulins (Ig), which are antibodies produced by plasma cells, to strengthen a compromised immune system (O'Horo &

Safdar, 2009). In a review discussing studies evaluating immunoglobulin treatments, including oral Ig, monoclonal antibodies, and polyclonal intravenous immunoglobulins, 77 patients were included, with a 26% relapse rate. Oral Ig was found to be the most effective and accessible for the general patient population, yet the study did not demonstrate a significant benefit over metronidazole, which is more cost-effective than Ig preparations. Another treatment that has been studied is the use of probiotics. Antibiotic-associated diarrhea, where the gastrointestinal (GI) microbiota is severely disrupted, allows overgrowth of virulent bacteria such as *C. difficile*. Probiotics attempt to remedy this by providing healthy microbes, which should already be present within a normal microbiome, to recolonize the colon and prevent dominance by pathogens. Most studies of probiotics in antibiotic-associated diarrhea have been preventative and have indicated some benefits in the treatment of CDI. Still, these studies have limitations, such as high relapse rates (66%) or benefit only when used in conjunction with high-dose vancomycin (O'Horo et al, 2013). The most significantly successful alternative treatment has been Fecal Microbiota Transplantation (FMT), which involves the placing of stool from a healthy donor directly into a patient's GI tract to normalize its microbiota composition. The delivery can be through the upper or lower GI route, which involves a nasogastric tube or colonoscopy, or through an oral capsule. FMT has high success rates as high as 80% with no recurrence but still comes with limitations. For instance, it is invasive, costly, and can be unappealing to patients due to its nature. Additionally, collecting and preparing donor samples is extensive with no systematic process in place (Wang et al., 2019).

Similar to the issue with therapeutics only having moderate success, the diagnostic tools for CDI are also often subpar. With the frequency of cases of CDI increasing, accurate and reliable diagnosis is important, as it affects the efficacy of treatments and recovery. However,

two reference standards served as hindrances to this process: cytotoxic assays and cytotoxigenic culture. Because these were ineffective and laborious to perform, these methods were mostly abandoned for rapid enzyme immunoassays (EIAs). Unfortunately, EIAs have suboptimal sensitivity and specificity, undermining this diagnostic due to high rates of false positives and false negatives. More recently, nucleic acid amplification tests (NAATs) have been developed to detect toxin genes, which do offer improved sensitivity over immunoassays, but fail to distinguish between CDI and asymptomatic colonization of the *C. difficile* bacterium, which still leads to unanswered questions (Wilcox, 2012).

Healthcare systems exhibit an inertia and slowness to change that can make disseminating new alternative treatments difficult. Resistance to change and action is a prevalent factor within medicine and is known as clinical inertia, often involving a failure to initiate or intensify a therapy according to evidence-based guidelines. The uptake of an evidence-based intervention in clinical practice can take on average 17 years before it becomes part of a routine practice (Medlinskiene et al., 2021). (O'Connor et al, 2005) propose three classes of symptoms leading to clinical inertia: factors related to providers, patients, and the system as a whole. The provider-related aspects are assumed to be the most common factors that relate to clinical inertia, with providers' lack of training or education, disagreement with the applicability of guidelines, or overestimation of the care they can provide. It is also seen that patient characteristics can be considered a major factor in clinical inertia (Aujoulat et al., 2014). Moreover, organization and systemic factors, such as stressful, overworked professional settings are linked to different contexts of care in clinical practice.

While researchers in the biomedical field are constantly innovating and discovering new technical information, the historical and socio-technical reasons behind the stagnation in CDI

treatment have not been elucidated. Understanding the history of this disease, as well as its treatments, is crucial in improving the way researchers innovate for the future. I intend to analyze the socio-technical reasons behind the stagnation in CDI treatment using the Diffusion of Innovation Theory, which aims to explore how new ideas, technologies, etc. are spread and adopted within a society (Rogers, 1962). I use this framework to uncover how new treatments get disseminated and barriers that exist, particularly within the biomedical research and healthcare system. I will also explore why innovations fail at times, and the communication channels that lead to this. The main factors within this framework are diffusion, innovations, communication channels, time, and social systems.

Methods

I employed a historical analysis approach to explore the timeline of CDI treatment evolution, as well as how research and public perception of both the disease and treatments have progressed. This analysis begins in 1935 when the *Clostridium Difficile* bacteria was discovered and continues into the present day to discuss the evolution of diagnostics, treatments, and current perceptions of the disease. I focused on secondary sources, such as historical reviews of the characterization of the *C. diff* bacteria, the evolution of treatments, and the current state of the disease. Additionally, I also utilized social studies that have been conducted about the patient and public perception of CDI and FMT, the most successful therapeutic alternative. I also extracted certain quotes from the media to illustrate how media portrayal of a disease can affect its perception among the public.

Analysis

There exists a negative perception of CDI among the general public in the US, which can hinder the diffusion of education and innovation related to the disease. Despite education efforts

and infection prevention policies, confusion, misunderstanding, and anxiety persists surrounding CDI and other healthcare-acquired infections. In a 2013 study of CDI, many people reported that they did not understand the infection or how it was treated, and would feel angry and afraid if they were to be infected. Many participants stated that they gained their information about CDI from media and television and voiced a significant distrust of healthcare workers. For example, there were concerns over the lack of information provided by healthcare organizations and staff about the disease, as well as about treatment options. Other anxieties that were commonly identified include information from healthcare workers failing to address concerns, exaggeration of information provided, and inability to comprehend information received. Additionally, many participants perceived a high risk of infection if they were in the hospital for an unrelated infection, and expected that they would be severely affected (Burnett et al., 2013). Certain preconceived notions about CDI exist due to the way in which people have learned about the disease. The communication channels for education regarding this disease are currently coming from things like media and television, rather than healthcare professionals or education systems.

The media portrayals of CDI have contributed to fear-mongering regarding the disease, contributing to the improper communication channels in which people learn about CDI. For example, journals and newspapers often represent the bacteria in a dramatized and panic-inducing way: “superbug” (Sweeney 2008), “terrifying”, (McAulay 2008) “horror”, (Bruce 2008) “aggressive” (Robertson 2008) and patients “succumbed to *C. difficile*” (Grant 2008).” These are all instances of vocabulary used to describe CDI, framing it in a way that evokes responses like fear and anxiety, rather than educating and preparing the public (Burnett, 2017). Sensationalized or alarmist reporting and language can contribute to stigmatization of the disease, and those that have been infected. This can also fuel skepticism in the healthcare

industry and turn patients away from alternative therapies or clinical trials. Additionally, according to the Diffusion of Innovation framework, ineffective communication channels can significantly impede the diffusion of innovation due to limited awareness, misinterpretation, lack of credibility, and limited reach. If media coverage is the only way people are educated about CDI, it can impede the dissemination of important information, resulting in reduced credibility of healthcare recommendations, and ultimately hindering the uptake of innovative approaches to managing disease.

While it can be argued that people who are fearful of CDI would be more likely to explore alternative treatments due to desperation and a desire to be healthy, the opposite effect is often seen. Unfortunately, a fear of disease is often accompanied by a fear of treatment and novel technology. Many of the alternative treatments available now, though more effective, are invasive and unpleasant, like fecal microbiota transplantation (FMT), which can deter individuals from pursuing them. Antibiotics are the method that has been used for the last 70 years and is a widely used treatment for a variety of infections, giving patients a sense of security, even if it is not the most effective treatment. Deploying new technologies, even when they are significantly better at treating infection, often faces barriers such as resistance to change from risk-averse individuals, compatibility issues with existing systems, regulatory constraints, and organizational policies. While the Diffusion of Innovation framework acknowledges that individuals' resistance to change coupled with regulatory constraints can impede the adoption of innovations, the framework has limitations in fully capturing the personal factors that influence technology adoption. While it highlights factors like organizational barriers, it may not adequately address the emotional and psychological aspects influencing individuals' decisions. Uncertainty, stemming from a variety of factors, can significantly influence personal health

decisions and perceptions surrounding health, which are not always accounted for in a theoretical framework.

Alternative therapeutics that have been shown to work better than antibiotics are not becoming widespread due to fear regarding the treatments and other barriers mentioned previously. The process of FMT involves collecting and processing donor stool and transplanting it into sick patients, usually through endoscopy or oral capsule. By nature, this is unappealing and unpleasant for patients. Endoscopy can be uncomfortable, invasive, and expensive. According to one study, concerns surrounding FMT included disease transmission and were followed closely by a response of "dirty" and "afraid" from participants (Park et al., 2016). FMT can have a high rate of disease transmission for immunocompromised patients, who are often the patients experiencing CDI. For those with normal immune systems, side effects of FMT can include abdominal discomfort, diarrhea, and fever, which are many of the same symptoms associated with CDI (Wang et al. 2019). FMT is an uncomfortable idea, and thus, fear has been gathered around the technology. Little to no communication about this technology is provided, unless a patient is actively participating in the treatment. Additionally, there is a certain "ick" factor that comes with the idea of what is essentially, a feces transplant. Although it is processed and technically and biologically clean, safe, and effective, the norms built into our social system hinder people from being willing to explore this treatment. Given this, it was found that people with children or with a college education or higher were more likely to agree to an FMT treatment with others (Park et al, 2016). Currently, there is also no systematic way to standardize donor samples and scale them to a large system, demonstrating what is currently an ineffective diffusion channel. This hinders the adoption of the technology, particularly when combined with the lack of education and emphasis on patient ease.

The negative perceptions surrounding both CDI and alternative treatments combined with barriers within clinical systems have made it difficult to advance research and adopt new treatments. Obstacles to accessing medicine are complex and exist at multiple levels within the healthcare system. For instance, patients who are younger, white, and have higher education are often prescribed newer medicines at a higher rate than others (Medlinskiene et al., 2021). Given that the majority of CDI patients are geriatric, they are experiencing the consequences of this bias; not being offered clinical trials at the same rate as younger patients creates a cycle of a lack of information and participation. Additionally, barriers exist not only on the patient level but also on the prescriber and organizational level. Without an incentive to move away from decades-long used methods, clinicians do not go out of their way to offer alternative options to most patients. This inertia can stem from things such as a lack of familiarity, concerns about efficacy, or a preference for the status quo.

While patient and organizational factors play a large role in the stagnation of CDI treatment, the clinicians and researchers who are in the role of innovators also have a hand in the issue. The *Clostridium difficile* bacteria were characterized successfully early on, and this rapidity and thoroughness of early discoveries may have inadvertently contributed to an early perception that there was nothing left to learn. The 1988 textbook, *Clostridium difficile: Its Role in Intestinal Disease* states:

> "Most of the important information regarding this microbe and the associated enteric infection is now known. ... There remain nuances of this disease that are poorly understood, but there is no doubt that this potentially lethal pathogen is now largely controlled and patients who have a life-threatening infection are now managed with diagnostic and therapeutic modalities that are extremely effective."

This created a false impression of CDI, as well as a clinical complacency that the disease was just a nuisance that could be easily managed, which has stifled new drug development (Gerding, 2009). Clinicians and researchers may have historically felt that the existing diagnostic and therapeutic modalities were sufficient to address the infection; however, given the rising cases of CDI, this is not the case. As a result, the impact of CDI on patient morbidity and mortality may have been underestimated, and a lack of awareness about the evolving nature of the disease has hindered innovation in CDI, perpetuating the stagnation of research in this area.

Conclusion

The innovation and deployment of CDI treatments have faced stagnation due to barriers within the complexity of the healthcare system, which has also affected the research and development of these therapeutics. The interplay between historical perspectives of CDI, systemic clinical inertia, and public perception of the disease has led to socio-technical conditions that hinder the diffusion of new therapeutics. Understanding these factors can help current researchers and clinicians avoid historical mistakes and clear false impressions of the disease. I intend for future developers in this field to use my research when they are innovating new medicines, techniques, or devices. By recognizing the historical context and systemic barriers within the healthcare system, developers can tailor their research to address specific challenges. I believe that elucidating the reasoning for barriers in complex systems like healthcare is a key step in removing these obstacles and improving accessibility for all. I also hope my research will inspire other scientists to consider accessibility and historical barriers to the application of their research and educate them to create technology that will be resilient and robust in the face of obstacles, such as understanding how to deal with clinical inertia or public fear.

Furthermore, this research serves as a call to action for scientists to educate themselves on the socio-technical landscape of CDI treatment and understand the nuances of the healthcare system. A large part of the reason behind the stagnation in treatment is that researchers and clinicians became too comfortable with the information that had already been discovered, incorrectly believing that no more work needed to be done regarding CDI. I hope this research emphasizes the need for thoroughness and seriousness regarding all diseases. Additionally, this work should inspire researchers to be courageous enough to explore alternative therapies like bacteriotherapy, rather than sticking to the status quo. Learning from our history can help us avoid the same mistakes, and inform our decisions for the future, so research like mine and others is exciting and important as it can help optimize the use of the plethora of medical technology to best serve patients of all backgrounds. By addressing the complex interplay of history, systemic barriers, and public perceptions, researchers can pave the way for more accessible and effective treatments for both CDI and other healthcare challenges.

Word Count: 3540

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