Designing an Ingestible Encapsulated Therapeutic for Resolving Recurrent *Clostridioides difficile* Infection

(Technical Project)

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

(STS Project)

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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

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). Despite this, treatments for colitis infections, which cause swelling of the large intestine and numerous gastrointestinal issues (Neurath et al., 2000), have remained unchanged for the last half-century. One of these diseases, caused by *Clostridioides difficile* (*C. diff*) bacterium, is an infection that is contracted primarily within healthcare-related settings and is the main 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 throughout the United States (Guh et al., 2020); one in 11 people over age 65 diagnosed with a healthcare-associated *C. diff* infection (CDI) die within one month (CDC, 2022). High-risk conditions for this infection include prolonged hospital stays, older age, weakened immune system, and, notably, recent antimicrobial therapy. Stomach pain, fever, severe diarrhea, and nausea are among the most common symptoms that come with CDI (Goudarzi et al., 2014). CDI is unique due to its high recurrence rates; around 1 in 6 CDI patients will contract it again in the 2-8 weeks following recovery. Current treatments for CDI exacerbate this cyclical frequency, exposing a need for better therapeutics (Baines & Wilcox, 2015). 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 research efforts, the scope of treatment for CDI remains limited, which is due to an interplay between scientific, societal, and technological elements. If

the situation remains as it is currently, patients, often in hospitals for unrelated health issues, will continue to contract CDI with high rates of recurrence and face intense symptoms without a source of relief. To address these concerns, I will propose a technical intervention through the development of a new therapeutic that is more accessible, affordable, and a permanent solution throughout this paper. I will also outline the historical contexts behind CDI treatments, and attempt to understand how this situation came to be through the use of historical STS frameworks and innovation studies. Using an STS perspective, I will delve into the sociotechnical factors contributing to the stagnation in *C. diff* treatment, highlighting the history of inertia within medical practice and socio-technical networks acting as barriers to the adoption of new, potentially more successful therapies.

Technical Project

Clostridium difficile infection remains a substantial worldwide burden on both healthcare systems and external communities despite significant research for years. Originally, this anaerobic bacterium was identified as a part of the gut flora of healthy infants in 1935 but was noted by researchers that it could be a source of disease in animals. After being properly characterized as a human disease-inducing bacterium in the 1970s, researchers began understanding the mechanisms of *C. diff.* CDI is transmitted by the oral-fecal route through spores, which in this case are dormant cells resistant to many environmental factors, like some disinfectants. After passing through the stomach, spores germinate in the duodenum and continue to grow in the cecum and colon, where toxins trigger a complex cascade of cellular responses to cause symptoms and inflammation. The ability of spores to colonize the intestine is greatly influenced by the host microbiota, antimicrobial agents, immune system, and other metabolites

(Smits et al., 2016). The first line of treatment for CDI is a collection of narrow-spectrum antibiotics, such as vancomycin, metronidazole, and fidaxomicin. Ironically, one of the most significant risk factors for acquiring CDI is recent antibiotic use, because it disrupts healthy gut microbiota communities, which are vital for normal function, particularly of the adaptive immune system. Increased use of antibiotics can have a multitude of negative impacts, such as reduced microbiota species diversity, altered metabolic activity, and antibiotic resistance (Ramirez et al., 2020). This creates a dangerous cycle of reinfection as well as an increased risk for patients in the hospital for unrelated conditions. After treatment of an initial episode of CDI, the chance of a recurrence within 8 weeks is 15–25%; for a patient with 1–2 previous recurrences, the risk of further recurrences is 40–65% (Smits et al., 2016). The economic burden of healthcare-associated CDI is significant due to the mortality, recurrence, and additional length of hospital stay, and exceeds $700 million annually in the US alone (Finn et al., 2021). This vicious cycle calls for innovations to address the needs of patients, and while research has made significant attempts, antibiotics remain the primary therapeutic. Currently, limited evidence supports the use of probiotics to treat CDI recurrence, and no effective immunotherapy is available to target the cascade of cellular mechanisms that are activated after spore colonization. One alternative therapy that has proved to be successful is fecal microbiota transplantation (FMT), which has approximately 81% success rate in treating multiple recurrent CDI. However, FMT is a non-standardized procedure still in clinical trial stages and the long-term consequences are unknown. Additionally, there is no effective system in place to coordinate and standardize fecal donors, and the transplant is administered through a pill or colonoscopic infusion, which can be uncomfortable, invasive, unappealing, and inaccessible.

To address this situation, I am proposing a novel bacteriotherapy that involves delivering a cocktail of healthy bacteria to the large intestine to restore normal gut flora and treat recurrent CDI. The bacterial community that will be used has been identified in previous work to be vital in restoring normal microbiota: a cooperative consortium consisting of *Bifidobacterium longum* ATCC 55813, *Escherichia coli* K12, *Roseburia intestinalis* DSM 14610, and *Streptococcus thermophilus* LMD-9. To be effective, this encapsulation must successfully form particles to fully enclose the aerobic bacteria and protect them from oxygen, as well as travel intact until the small intestine. This involves surviving through harsh environments such as the esophagus, stomach acid, and bile, yet breaking down as it approaches the trypsin within the intestinal tract. To do this, I will test granular hydrogels with various synthesis methods and base materials such as hyaluronic acid, polyethylene glycol, and carboxymethylcellulose, all of which have favorable properties to travel within the body (Knipe, 2015). After the successful completion of encapsulation and *in vitro* experiments, the biologic will be tested in mouse models to study the efficacy of the therapeutic in resolving CDI. Long term, the goal is to reach the point of clinical trials and be available for treating patients. One important constraint of this project is ensuring affordability and accessibility, which sets this apart from other alternative therapeutics for CDI. A major patient population of this infection is geriatric individuals, who often have a difficult time chewing or swallowing and are opposed to highly invasive or expensive treatments. Given this, our encapsulation method will be a pill-alternative method that can easily dissolve in the mouth or water, like a film or jelly. This deliverable will not only address the medical shortcomings of previous treatments, but it will also resolve the stagnation in this field and provide an accessible, affordable therapeutic for CDI patients.

STS Project

When colitis infections were first studied in the 1950s, vancomycin was used as a standard treatment for this condition (Bartlett, 2008). Today, vancomycin is still one of the first antibiotics administered for *C. diff* infection (Khanna & Gerding, 2019). The stagnation in the development of CDI treatments is not due to a lack of effort on the part of researchers, or limited technology for experimentation. Rather, various sociotechnical factors and systems impact how the disease is framed, as well as how it is researched and funded. The sociotechnical network surrounding current treatments, such as established clinic guidelines and medical inertia, will be explored as they have acted as a hindrance to the wide use of alternative, more successful treatments. Additionally, I will also discuss the way CDI is perceived, which is often in an unappealing way due to the nature of infection and its symptoms, resulting in less attention and incentive for funding from pharmaceutical companies.

To conduct this research, I will employ the theory of Social Construction of Technology (SCOT), developed by Pinch and Bijker. The main argument of this theory is that technology is not an objective, isolated entity but rather closely involved with the social world and constructed by the cultural, political, and economic context in which it was created. SCOT also raises the idea that technology can be interpreted and shaped in flexible ways by different social groups, calling for a more nuanced understanding of technology outside of pure scientific innovation (Pinch and Bijker, 1984).

I propose that within the healthcare and research systems in the US, there is a history of societal and institutional factors that have contributed to the stagnation of CDI treatments. Using this framework, I will be considering how the interplay between social constructs and technological development has affected institutional standardization, pharmaceutical influences, and patient factors. Resistance to change and action is a prevalent factor within the healthcare system as a whole and is known as clinical inertia (Aujoulat et al., 2014). This idea will be applied to research and innovation

to uncover the medical guidelines and professional habits that have hindered progress in CDI treatment. Additionally, there is an economy of science and technology that plays a role in the development of cures for diseases. The lack of financial incentives from pharmaceutical companies, which prioritize more "attractive" diseases with larger coverage, is also a critical player in why *C. diff* treatments have not progressed.

Alongside SCOT, I will also employ an STS theory known as Diffusion of Innovation (DOI), developed by Everett Rogers, that explains the way in which new technologies are adopted by individuals and societies, providing information about how these innovations are taken into different social systems. In this, four main elements are highlighted: innovation, communication channels, time, and social system (Salwen, 2008). DOI can elucidate how innovations spread and emphasize factors that either exacerbate or hinder their implementation. The persistence of antibiotics as the primary treatment for CDI exemplifies resistance to innovation, particularly due to the medical community's extensive reliance on these types of treatments. I will also highlight aspects of the communication channels within this space, notably education and awareness, and how limited information perpetuates the emphasis on traditional therapies.

Failing to understand the nuances and sociotechnical reasoning behind the stagnation of CDI treatments will facilitate the vicious cycle that CDI currently poses on both patients and the healthcare system. Using the aforementioned theories, I will reveal the historical and social barriers that have kept *C. diff* research from progressing over the last 50 years.

Research Question and Methods:

The question I aim to answer is: What are the historical and social reasons behind why the treatments for *Clostridiodes difficile* infection have remained virtually unchanged since antimicrobial therapeutics have been developed, even though they are not effective at resolving this disease? Understanding the history of CDI and what research has been conducted is important for

contemporary medicine as it sheds light on what conditions have ignited or hindered progress from occurring. Additionally, analyzing the sociotechnical network in place in this specific field will provide significant insight into how we can create better systems to facilitate innovation. To answer this question, I will a literature review, use STS frameworks, and explore case studies, both in historical and present contexts. Additionally, I will also interview a local woman who has had recurrent CDI for the last 20 years, contracting it at least 4 times to understand a firsthand patient experience, as well as gather information about what kinds of therapeutics are offered and how patients are educated about CDI. Finally, I will employ STS theories such as Social Construction of Technology and Diffusion of Innovation to understand how the sociotechnical networks surrounding CDI and its perceptions have contributed to the current state of stagnation.

Conclusion

In my technical project, I plan to develop a therapeutic that will deliver a community of cooperative bacteria to the large intestine to restore healthy gut microbiota and combat recurrent *Clostridioides difficile* infection through the use of synthesized biomaterials and specific targeting technology. In my STS project, I will uncover the historical and sociotechnical reasons behind why CDI treatment has remained unchanged and reliant on the same antibiotics that were discovered decades ago even though it does not successfully resolve CDI. These deliverables will provide a meaningful understanding of the socio-technical network that is present within medical research and how it can hinder innovation. This research serves as a reminder that addressing complex medical challenges requires an integration of scientific innovation and an understanding of the sociotechnical dynamics that shape the healthcare landscape.

Word Count: 2152

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