Thesis Project Portfolio

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* Infection Treatments

(STS Research Paper)

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Sociotechnical Synthesis

My technical and STS research are both concerning the landscape of treatments of *Clostridium difficile* infection (CDI), a healthcare-acquired infection which affects the gastrointestinal tract. My STS worked explored why there has been a historical stagnation and lack of progress in treatments, even though current treatments are not adequate. My technical research attempts to create a solution to this problem through development of an alternative therapy for resolving recurrent CDI. Both projects are significantly intersectional and intertwined with each other, with the STS problem informing how I can conduct effective technical research in the laboratory to create a better therapeutic that resolves not only CDI, but the problems with current treatments.

Clostridioides difficile (*C. diff*) is an infectious bacterium that is contracted within 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. It has an estimated prevalence of 400,000 cases annually, and growing incidence and mortality rates. 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 flora is disrupted, increasing susceptibility to C. diff infection. 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 rates5. 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. Given this, the goal of my technical project is to develop a microbial therapeutic that will deliver a "healthy" community of anaerobic bacteria to the large intestine that can end the cycle of recurrent CDI for patients. To achieve this goal, I developed an encapsulation method and material that will keep the bacteria alive and contained until they reach the large intestine, where it is released. The bacterial community that will be used has been identified in previous work: a cooperative consortium consisting of *Bifidobacterium longum ATCC 55813, Escherichia coli K12, Roseburia intestinalis DSM 14610, and Streptococcus thermophilus LMD-9.* This consortia was encapsulated in a carboxymethyl cellulose-based hydrogel, with the addition of a custom peptide crosslinker that degrades in contact with the enzyme trypsin, which is located in the intestinal tract. Stability and degradation studies were conducted on *E. Coli* encapsulated in this material under physiologically relevant temperatures and pH levels. Under all conditions, viable bacteria were able to be recovered and re-cultured, demonstrating that the material effectively protects and encapsulates the bacteria.

My STS research aims to elucidate the sociotechnical reason behind why there is a historical stagnation in *C. difficile* treatment research. In order to analyze this problem, I studied the historical timeline of CDI treatment, current alternative therapies being researched, and the public perception of the disease. I used the Diffusion of Innovation framework, which explores how new ideas, technologies, etc. are spread and adopted within a society. I used 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. In my research, I employed a historical analysis approach, beginning in 1935 when the *Clostridium Difficile* bacteria was discovered and continued into the present day to discuss the evolution of diagnostics, treatments, and current

perceptions of the disease. Using this, I found that media portrayal, often sensationalized and alarmist, serves as many people's many sources of education regarding this disease, contributing to a fearful view of CDI. Not only are people fearful of the disease, they are also fearful of alternative therapeutics, which while more effective at resolving CDI, are more unappealing and invasive. Additionally, barriers within the clinical system, on the patient, physician, and systemic level have made it difficult to both advance research and adopt new treatments. I found evidence that *C. diff* bacteria was characterized early on in its discovery, which may have inadvertently 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. In order to address these issues, I suggested that introducing a historical and sociotechnical perspective among researchers could help clear misconceptions and create a better understanding of the context of CDI, motivating new innovations. The paper may serve as a call to action among scientists to educate themselves on the sociotechnical landscape of CDI treatment and understand the nuances of the healthcare system.

Conducting both technical and sociotechnical research surrounding CDI therapeutics was crucial in creating a well-rounded picture of the disease, and helping me understand why I was working in the lab to create an alternative treatment. Additionally, it provided context surrounding the disease and helped me be aware of what issues to find solutions and avoid repeating mistakes of the past. Conducting research using the Diffusion of Innovation framework helped me understand the broader context in which treatments are developed, deployed, and utilized. This includes factors such as healthcare systems, clinical practices, patient perspectives, and socio economic considerations, all of which helped uncover barriers to the adoption of new treatments. The technical and STS projects are directly interconnected and mutually informing;

my technical research aims to identify and test a promising new therapeutic candidate and the STS work can help understand how this candidate will be received and implemented in the real world. Conversely, sociotechnical research can highlight where there are unmet needs or gaps in healthcare, informing the direction of technical work. By approaching both perspectives, researchers can develop more holistic approaches to addressing biomedical challenges like CDI treatment. This interdisciplinary approach is crucial for overcoming stagnations in treatments and ensuring that new innovations are not only effective, but accessible to all.