**Exploring mRNA Technology for the Development of a Novel Tuberculosis Vaccine**
(Technical Paper)

**The Impact of Socioeconomic Factors on Access to Rapidly Developed Medicines in Lower-Income Countries and Strategies for Reducing Global Disparities**
(STS Paper)

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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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**How do socioeconomic factors impact access to rapidly developed medicines in lower-income countries, and what strategies can be implemented to reduce these disparities globally?**

## Introduction

The sociotechnical problem of this project lies in the intersection of global health advancements and socioeconomic inequities that prevent fair access to life-saving vaccines and other treatments. The technical work aims to improve global health by creating a tuberculosis (TB) vaccine with mRNA vaccine technologies, ultimately striving to eliminate TB as a global health threat and decrease related mortality. However, a broader challenge remains in allowing these vaccines to reach the populations that need them the most, particularly in low-income countries such as Pakistan, Nigeria, Bangladesh, the Democratic Republic of the Congo, and Myanmar (World Population Review, 2024). The STS work addresses the social and structural barriers to healthcare access that often deepen existing inequities in the global health system. The COVID-19 pandemic highlighted the severe consequences of global inequities, with some countries facing shortages or delayed access to vaccines while others procured more than enough vaccines for their populations (Pushkaran et al., 2024). This disparity was exacerbated by vaccine nationalism, intellectual property barriers, and unequal healthcare infrastructures (Upton, 2024). This project aims to prevent such inequality from recurring, ensuring that vaccines like those for TB and COVID-19 are accessible to and affordable for all countries, irrespective of their economic or social barriers. The overall sociotechnical challenge is to design and deploy an effective TB vaccine while ensuring it is integrated into a system that promotes equity in healthcare to prevent future global health crises and achieve the ultimate goal of global TB elimination.

**Exploring mRNA Technology for the Development of a Novel Tuberculosis Vaccine**

Vaccines have evolved significantly since their introduction in 1796, yet there is an increasing demand for large-scale production and novel vaccine development (Wang et al., 2021). mRNA vaccines hold potential for fighting both cancer and infectious diseases, offering advantages in safety, efficacy, flexibility, and commercial scalability compared to traditional vaccines (Schlake et al., 2012). It is critical to improve current delivery mechanisms, specifically lipid nanoparticles (LNPs) (Matarazzo & Bettencourt, 2023). LNPs encapsulate mRNA via rapid mixing, protecting it from enzymatic degradation and facilitating its release into the cytoplasm for antigen synthesis (Hou et al., 2021). Because any protein can be encoded and expressed by mRNA, this process allows for manufacturing vaccines targeting various diseases, including cancers, influenza, SARS-CoV-2, HIV, and tuberculosis (TB) (Schlake et al., 2012). TB is of particular interest given its status as a leading cause of death in low- and middle-income countries and the lack of an effective vaccine. mRNA technology simplifies the development of vaccines against complex infectious diseases like TB (Matarazzo & Bettencourt, 2023). Our work aims to replicate and optimize the mRNA vaccine production process, focusing on the LNP delivery system and rapid mixing technique, using TB as a case study.

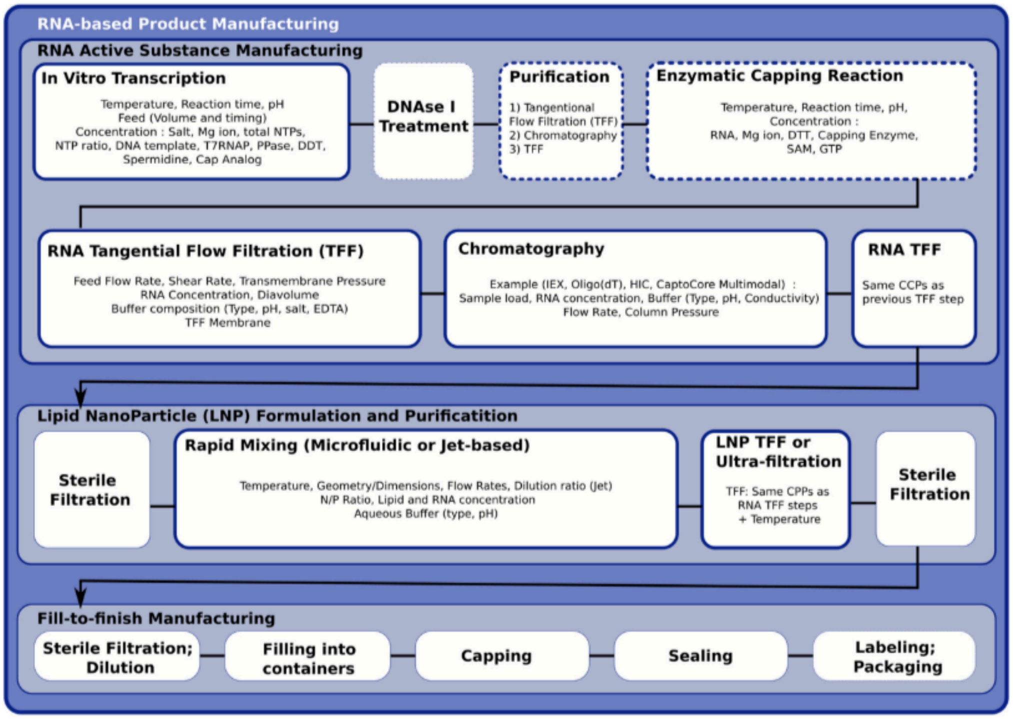


**Figure 1.** Process Flow Diagram of the mRNA Vaccine Manufacturing Process (Daniel et al., 2023)

Our process will be designed based on the research of Daniel et al., 2023 (Fig. 1). The research identifies three main phases of RNA vaccine manufacturing, which include manufacturing the RNA active substance, formulating and purifying the lipid nanoparticles, and the final fill-to-finish. Our design will focus exclusively on the mRNA and lipid nanoparticle synthesis and purification, ending at the sterile filtration step identified in Figure 1. The feeds to our process will include all necessary nucleotides, enzymes, and lipids to synthesize mRNA and lipid nanoparticles at an industrial scale. Our finished product will be a purified and sterilized suspension of lipid nanoparticles formulated with a desired mRNA sequence.

Our mRNA vaccine manufacturing process will involve several unit operations. A batch-fed bioreactor will perform both the process's in vitro transcription and enzymatic steps (DNA degradation and capping). For purification, we will employ a combination of chromatography methods, including affinity resin-based, anion-exchange, and hydrophobic interaction chromatography. These methods will purify full-length mRNA from impurities such as DNA fragments, enzymes, unreacted nucleoside triphosphates, unreacted caps, incomplete mRNA sequences, etc. (BioPhorum, 2023). Tangential-flow filtration (TFF) will be used with chromatography to purify and concentrate mRNA after transcription, enzymatic capping, and lipid nanoparticle (LNP) formation before fill-to-finish. Sterile filtration will be implemented in three stages: before LNP formation, after LNP formation, and before filling. We will use jet-based or microfluidic mixing to encapsulate the mRNA product to form the LNPs. These processes will ensure that our final mRNA product meets quality standards and is safe for patients.

Regarding computation tools and software, we will use Aspen Plus to model applicable process sections. We will use MATLAB or Python for more detailed calculations, data analysis, and process modeling that cannot be done in Aspen. We may also explore alternative software options, such as COMSOL, for specific fluid dynamics and heat transfer simulations. To gather necessary design data, we will seek to understand current mRNA manufacturing processes and review papers and articles on lab-scale operations. We also plan to consult experts who have industry experience to gain insights into challenges and opportunities specific to our process. Essential data will include but are not limited to, mRNA synthesis "recipes" (amount of base pairs, enzyme concentrations, etc., based on sequence length), LNP formulation details (lipid combinations and ratios for achieving desired particle size and properties), dosing and market size information (based on TB) (National Institutes of Health, 2023), and information on potential solvents and adjuvants, including thermodynamic properties. By leveraging a wide range of computation tools and reliable data sources, we aim to develop a safe, feasible mRNA therapeutic manufacturing process.

**The Impact of Socioeconomic Factors on Access to Rapidly Developed Medicines in Lower-Income Countries and Strategies for Reducing Global Disparities**

The STS portion of the project focuses on healthcare inequities in lower-income countries (LICs), explicitly answering the question: How do socioeconomic factors impact access to rapidly developed medicines in lower-income countries, and what strategies can be implemented to reduce these disparities globally? Lower-income countries include nations with a gross national income (GNI) per capita of $1,025 or less. In comparison, lower-middle-income countries (LMICs) have a GNI per capita between $1,026 and $3,995, upper-middle-income countries (UMICs) are between $3,996 and $12,375, and high-income countries (HICs) are $12,376 or more (The World Bank, 2019). These financial disparities are vital drivers of unequal access to healthcare resources, like vaccines. The United Nations strives to attain safe and affordable healthcare services for the global population. They are working to address these disparities, citing AIDS, TB, and malaria as some of the infectious diseases they want to end by 2030 (United Nations, 2024). The World Health Organization (WHO), among other international groups, promotes universal health coverage during public health emergencies, listing "improve access to essential medicines and health products" as one of their main goals. They believe access to healthcare is a fundamental human right that can increase community cohesion and economic productivity (World Health Organization, 2024). Addressing healthcare inequities will require both international cooperation and local strategies. My work aims to improve healthcare distribution and awareness in LICs to advance global health and decrease infectious disease and mortality rates.

To address this question, I will use the COVID-19 pandemic as a case study to examine what socioeconomic factors contributed to the vaccine inequities that arose. The COVID-19 vaccine was developed and approved in less than 12 months, an unprecedented achievement in the history of medicine. However, this quick turnaround exposed significant global healthcare inequities, mainly due to the prioritization of HICs' needs over the world's (Wei, 2023). Bilateral agreements between HIC governments and vaccine manufacturers secured large quantities of vaccines for HICs and were a significant cause of the unequal vaccine procurement issues for LICs (Upton, 2024). Even today, according to the WHO, countries with the lowest COVID-19 vaccination rates mainly include LICs: Burundi, Yemen, Papua New Guinea, Haiti, and Madagascar, among many others (World Health Organization, 2023). These inequities are not solely from economic factors, also facing social and infrastructural barriers. Vaccine hesitancy and healthcare readiness significantly affected the allocation and affordability of vaccines in many nations (Upton, 2024).

The COVID-19 pandemic and vaccine will be used as a case study to examine the impact of socioeconomic factors on the supply chains in LICs and HICs. I will use commodity chain analysis (Bair, 2008) to explore the actors and networks involved in the distribution of vaccines, looking at how financial and social powers shape the process. This includes examining every step of production, starting from the relationship between multinational pharmaceutical companies and HICs and uncovering the bilateral agreements that helped with procurement. I will then observe pharmaceutical infrastructure and transportation networks within LICs compared to HICs to highlight distribution differences. I will evaluate the response of international organizations, including an assessment of the strengths and weaknesses of COVAX, a global initiative created by the WHO to procure and distribute COVID-19 vaccines to LICs (Pushkaran et al., 2024). Lastly, I will use healthcare readiness indexes and vaccination rates throughout the pandemic to study the preparedness and response of national governments and healthcare systems in LICs and HICs. The framework of intersectionality (Crenshaw, 1989) will also be used to see how the distribution and use of vaccines reflect societal power dynamics, both internationally and domestically. This will require comparing national income status, government response, and citizen reaction between LICs and HICs. To address these elements, I will use published global health security indexes, vaccination rates and timelines, healthcare education reports, and vaccine willingness studies. This analysis should highlight the economic differences between countries that contribute to unequal vaccine distribution, as well as domestic issues like healthcare education. I will then propose strategies to address these power dynamics and mitigate the issue of vaccine nationalism, focusing on addressing distribution bottlenecks, improving infrastructure, and expanding healthcare education as critical areas of need.

**Conclusion**

The technical piece of my project focuses on designing a process to produce an mRNA TB vaccine with an emphasis on improving the LNP delivery system. The STS portion will explore how socioeconomic factors impact access to rapidly developed medicines like vaccines in LICs and propose strategies to reduce these global disparities. Using the COVID-19 pandemic as a case study, I will examine the factors contributing to healthcare inequities through commodity chain analysis and intersecting structures of power as STS frameworks. Commodity chain analysis will be used to examine pharmaceutical companies, international organizations, and national healthcare systems, assessing the complex network from development to distribution. Intersecting structures of power will be used to highlight socioeconomic disparities within and between nations, affecting vaccine distribution, access, and public response. Insights gained from the STS research will guide the ethical aspects of the technical work, ensuring access to our TB vaccine in LICs by prioritizing distribution and education. This is especially crucial, as five of the eight countries with the highest TB infection rates are LICs (World Population Review, 2024). Ultimately, we aim to design an effective TB vaccine that can be integrated into an equitable healthcare system, ensuring global access and supporting the worldwide effort to eliminate TB.

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