Thesis Project Portfolio

Industrial Scale Production of the R21c/Matrix-M Malaria Vaccine for Sub-Saharan Africa

(Technical Report)

Analyzing the Role of the 1996 Pfizer Meningitis Clinical Trial as a Vaccine Hesitancy Enhancer in Nigeria

(STS Research Paper)

An Undergraduate Thesis

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Executive Summary

Malaria is one of the leading causes of death in the world, with the number of cases increasing from 227 to 241 million from 2019 to 2020. This disease, mediated by mosquitos, is prevalent in regions around the equator, with the bulk of cases in sub-Saharan Africa (SSA), where 25% of child deaths are due to malaria (Price et al., 2020; Zekar & Sharman, 2022). While there are no currently approved malaria vaccines that meet the World Health Organization's guideline of 75% efficacy (World Health Organization, 2022), the novel malaria vaccine, R21c/Matrix-M, has surpassed this threshold during clinical trials. The goal of my technical project is to develop an industrial pipeline for the production of this promising malaria vaccine candidate, with the desire to immunize the majority of children in SSA. However, several barriers that prevent the effective distribution of vaccines in SSA exist. As a result, to better understand how we can overcome one of these barriers, vaccine hesitancy, I chose to perform a case study on vaccine hesitancy in Nigeria. Specifically, I aimed to understand how events in Nigeria's past, specifically the 1996 Pfizer Meningitis Clinical Trial, have strengthened vaccine hesitancy in Nigeria, and by doing so, I also identified potential methods to make vaccination campaigns more effective. My analysis provides the groundwork for identifying key campaign techniques and will ultimately help us overcome vaccine hesitancy as a barrier to immunization against malaria.

In the technical portion of my thesis, my team designed an industrial process to produce the R21c component of our malaria vaccine to fully immunize 28 million babies and 40 million children under five years of age in SSA per year, with the ultimate goal of producing 272 million vaccines per year. Our manufacturing process involves three major steps: upstream, downstream, and formulation & fill-finish. Upstream involves fermenting the yeast *Pichia pastoris*, which is

genetically engineered to produce the R21c protein under exposure to methanol. In downstream, the fermentation products undergo purification processes, including centrifugation, high-pressure homogenization, depth filtration, diafiltration, ultrafiltration, Capto Core 700 size-exclusion chromatography, and C-tag affinity chromatography, during which time the R21c proteins assemble into their final vaccine-like particle (VLP) form. In the final step, formulation & fill-finish, the product undergoes sterile filtration, followed by vial filling and lyophilization to prepare the vaccine for distribution. Resuspension in the adjuvant Matrix-M will occur at vaccine administration sites. An economic assessment of our process suggests that if we sell our vaccines at the Gavi-mandated ceiling price of $3/vaccine, we will make a substantial profit regardless of if a higher efficacy vaccine arrives on the market or if barriers to distribution hinder the fraction of the vaccines we ultimately sell.

For my STS research, I used Actor-Network Theory to analyze how the 1996 Pfizer Trovan clinical trial in Kano, Nigeria led to the strengthening of the country's vaccine hesitancy network, which is a major contributing factor to Nigeria's status as one of the leading countries in child mortality due to vaccine-preventable diseases (Mahachi et al., 2022). This high hesitancy is due to distrust in Western institutions and the central Nigerian government. Pre-1996, the aftermath of British colonialism played a significant role in forming such attitudes. In 1996, the clinical trial, which operated without informed consent and resulted in patient deaths (Stephens, 2000), enhanced, with the help of religious leaders, these negative perceptions of Western institutions and the government. However, the strength of influence that these religious leaders have may be used to destabilize the hesitancy network. My research indicates that vaccination campaigns can become more effective by having religious leaders advocate for vaccines and their safety to the leaders' constituents.

Working on my technical and STS research concurrently has been valuable in guiding my projects. Through my technical work, I have learned about the regulatory guidelines that govern the purification and production process, as well as the storage and distribution guidelines, and consequently identified possible issues in our product approval and distribution process. Through my STS work, I have developed an understanding of my malaria vaccine product in the context of the population I am serving (SSA). For example, we understand that vaccine hesitancy exists and will likely prevent us from distributing our vaccine to everyone. As a result, we designed our plant to ensure that our process is economically viable regardless of whether we sell all of our vaccines. We also understand that vaccine hesitancy, the main focus of my STS work, is not the only barrier. Infrastructure issues may prevent us from distributing vaccines to more rural parts of SSA that lack the necessary cold storage and transportation capabilities. However, understanding these limitations also guided our choice of South Africa as our plant location, which will minimize the need for extensive transportation infrastructure, as well as distance the vaccine from connections to Western institutions, of which many Africans are wary. Ultimately, working on my projects simultaneously was valuable as both are deeply intertwined: without understanding vaccine hesitancy in our target population, we cannot effectively design and distribute the R21c/Matrix-M vaccines.

Works Cited

Mahachi, K., Kessels, J., Boateng, K., Jean Baptiste, A. E., Mitula, P., Ekeman, E., Nic Lochlainn, L., Rosewell, A., Sodha, S. V., Abela-Ridder, B., & Gabrielli, A. F. (2022). Zero- or missed-dose children in Nigeria: Contributing factors and interventions to overcome immunization service delivery challenges. *Vaccine*, *40*(37), 5433–5444. https://doi.org/10.1016/j.vaccine.2022.07.058

Price, R. N., Commons, R. J., Battle, K. E., Thriemer, K., & Mendis, K. (2020). Plasmodium vivax in the Era of the Shrinking P. falciparum Map. *Trends in Parasitology*, *36*(6), 560–570. https://doi.org/10.1016/j.pt.2020.03.009

Stephens, J. (2000, December 17). *Where Profits and Lives Hang in Balance*. http://www.washingtonpost.com/wp-dyn/content/article/2008/10/01/AR2008100100973.html

World Health Organization. (2022). *Progress on the health-related Sustainable Development Goals and targets in the Eastern Mediterranean Region, 2020*. World Health Organization. Regional Office for the Eastern Mediterranean. https://apps.who.int/iris/handle/10665/361800

Zekar, L., & Sharman, T. (2022). Plasmodium Falciparum Malaria. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK555962/