Industrial Scale Production of R21/Matrix-M Malaria Vaccine for Sub-Saharan Africa;

How the Lack of Capital and Infrastructure in Developing African Countries Has Influenced COVID-19 Vaccine Distribution

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in William Wonsik

By
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October 27, 2022

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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

Malaria is a severe and potentially fatal disease caused by a parasite and transmitted by infected mosquitoes. Currently, malaria affects approximately 40% of the world's population and is endemic in over 90 countries (Zekar & Sharman, 2022). While malaria is worldwide, in 2018, nineteen African countries and India contained 85% of the cases (Zekar & Sharman, 2022). To slow the spread of malaria, and eventually eradicate it, an effective and available malaria vaccine is needed.

Currently, RTS,S/AS01, the only malaria vaccine available, has a 36% efficacy in children (5-17 months at receipt of vaccine) after 48 months (Olotu et al., 2016). The low efficacy of the vaccine signifies that malaria is likely to continue to spread. To address the technical deficiencies, we will propose a process design to produce a new, more effective malaria vaccine developed by Oxford.

However, while working on the project, I found infrastructural, economic, and political factors present that have an influence on the eradication of diseases in developing countries. Specifically, in 1955 the World Health Organization (WHO) began a Global Malaria Eradication Program (GMEP) (Nájera et al., 2011). However, the program failed 14 years later due to a lack of infrastructure and economic support (Nájera et al., 2011). The program failure is eerily similar to the current COVID-19 vaccine distribution. As of June 2021, about 85% of COVID-19 vaccine doses administered were in developed countries, while only 1% of Africa's population was vaccinated (Asundi et al., 2021). If this disparity continues, then the eradication of COVID-19 will fail because of the lack of vaccine availability in developing countries.

To effectively promote the production of the R21/Matrix-M vaccine for high risk malaria areas, both the technical and social aspects of vaccine manufacturing and distribution must be addressed. Below I outline the technical process for producing a new, more effective malaria

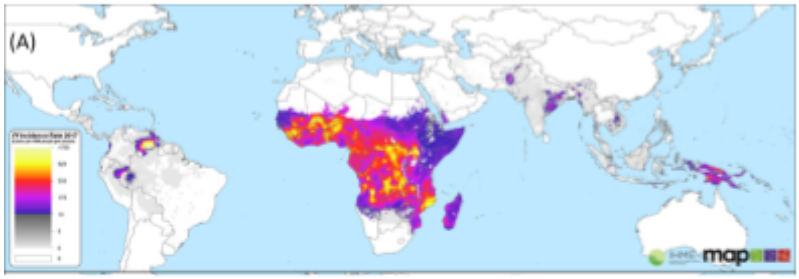
vaccine. I also utilize actor-network theory to analyze how the lack of capital and infrastructure in developing African countries has contributed to insufficient COVID-19 vaccine distribution.

Technical Project

In 2019, there were 228 million reported cases and 405 thousand deaths as a result of malaria, which remains one of the leading causes of morbidity and mortality in the developing world (Zekar & Sharman, 2022). In particular, Sub-Saharan African countries carry the majority of the malaria cases caused by *Plasmodium falciparum* (Figure 1), the parasite implicated in over 90% of world mortality due to malaria. The disease is spread via the *Anopheles* mosquito vector, which allows the parasite to enter the bloodstream and lyse host red blood cells during replication (Talapko et al., 2019). The infection results in high fevers, nausea, and muscle pain, among other symptoms. Severe malaria cases may result in severe anemia, comas, and respiratory distress. Although the drug artemisinin can completely eradicate the infection from the blood, due to drug resistance, *P. falciparum* can persist in the blood asymptomatically, causing recrudescence and serving as a source of further parasite spread (Cowman et al., 2016). As a result, there is a need for an effective malaria vaccine.

Figure 1

Frequency of P. falciparum Malaria Cases in 2017



Note. This figure demonstrates that while there are cases elsewhere, the primary regions in the world with a high incidence rate of P. falciparum malaria are Sub-Saharan African countries. Adapted from 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

Currently, the RTS,S/AS01 vaccine, developed by GlaxoSmithKline, is the only approved vaccine for malaria that was recommended for widespread use in endemic regions (D'Souza & Nderitu, 2021). The vaccine is a virus-like particle (VLP) that presents circumsporozoite protein (CSP), a protein on *P. falciparum* that is critical for infecting cells, by linking it to an unrelated antigen. AS01, a saponin-based adjuvant, is added to enhance vaccine efficacy (Nadeem et al., 2022). Unfortunately, clinical trial data demonstrate that at 48 months following the initial three-dose vaccination, the vaccine has only a 36% efficacy in children (5-17 months at receipt of vaccine) and a 26% efficacy in infants (6-12 weeks at receipt of vaccine). The efficacy further declines over time (Olotu et al., 2016).

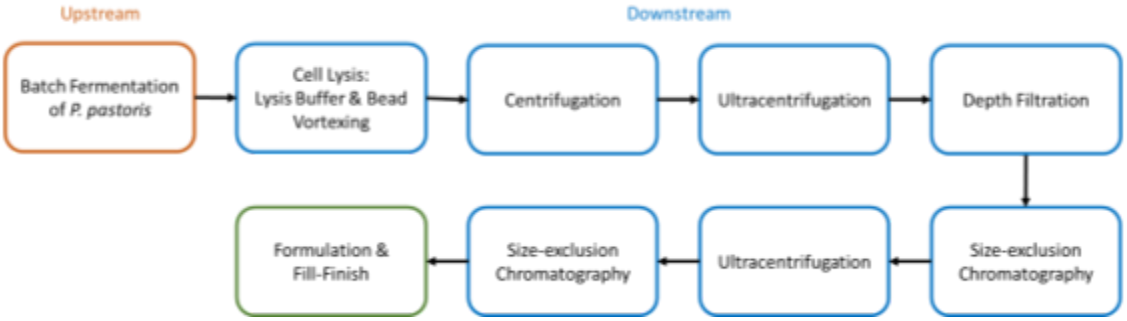
Recently, scientists at Oxford University developed the first vaccine to meet the World Health Organization's goal for 75% efficacy. Known as R21/Matrix-M, the vaccine is a pre-erythrocytic malaria vaccine that improves the RTS,S/A01 vaccine design. By modifying vaccine synthesis to increase the proportion of CSP, Oxford scientists were able to develop a more immunogenic VLP (Collins et al., 2017). Recent clinical trial data shows that 24 months after initial vaccination, the R21 vaccine has an 80% efficacy against malaria in children (5-17 months at receipt of vaccine) when mixed with Matrix-M, another saponin-based adjuvant (Datoo et al., 2022). Additionally, R21/Matrix-M is easier to develop than RTS,S/A01, due to its cheaper and more modern design (Mandavilli & Cheng, 2022). Currently, the vaccine is manufactured by the Serum Institute of India, allowing for the production of R21 to be nearly 30 times greater than RTS,S (Ledford, 2022). Although the vaccine is still undergoing clinical trials to confirm efficacy, R21/Matrix-M is a promising candidate for widespread use.

In anticipation of vaccine approval, this project aims to develop a cost-effective process to manufacture single doses of R21/Matrix-M for use in preventing malaria infections in

Sub-Saharan Africa. The process will involve industrial scale upstream, downstream, formulation and fill-finish stages (Figure 2). Upstream processing will include batch fermentation with *Pichia pastoris*, which is critical for R21 production. In downstream processing, the yeast cells will first be lysed using chemicals and bead vortexing, allowing the CSP fusion proteins to self-assemble into VLPs. Subsequently, the lysed material will go through centrifugation, followed by depth filtration, and then two cycles of ultracentrifugation and size-exclusion chromatography to purify the particles (Collins et al., 2017). For formulation and fill-finish, the R21 protein particle will be mixed with Matrix-M, which will be acquired from Novavax, at a 1:10 ratio (Datoo et al., 2022), resulting in the final product. The project will conclude with an economic and feasibility analysis.

Figure 2

Simple Process Flow Diagram of Proposed R21/Matrix-M Manufacturing Process



Our team will complete the design project over two semesters in CHE 4474 and CHE 4476. We plan to meet weekly to review progress and assign future work. Additionally, we will meet biweekly with Professor Eric Anderson, the chemical engineering capstone faculty advisor, to receive feedback and guidance. We will also consult Professor Michael King, an industry expert on vaccines, and Professor Giorgio Carta, a leader in bioseparations, for further advice. As R21/Matrix-M is a new vaccine still in clinical trials, there is limited available data on its

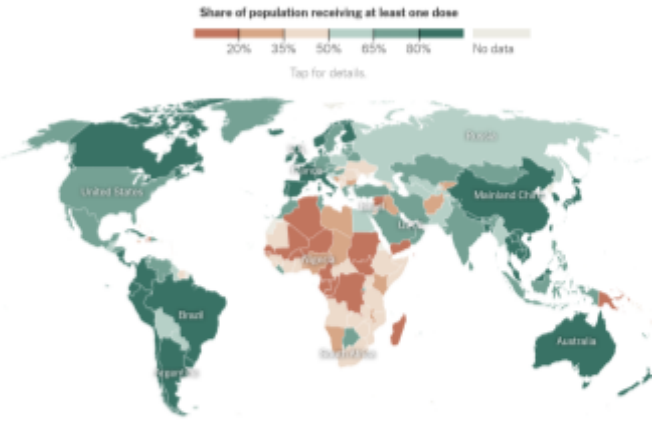
large-scale manufacturing. As a result, our team will consult Collins et al., which documents the methodology for lab-scale vaccine production, and documentation on the production of VLP vaccines that use technologies similar to those in R21.

STS Topic

In 2021, the World Health Organization (WHO) declared a target of 70% Covid-19 vaccination coverage by mid-2022 (World Health Organization, 2022). However, by June of 2022, only 30% of WHO's member states had reached the 70% goal and in developing countries, only 37% of healthcare workers had completed their primary vaccination (World Health Organization, 2022). Additionally, as seen in Figure 3, 33 countries, mostly developing countries located in Africa, have less than 35% of their population with at least one dose of a COVID-19 vaccine in October 2022 (Holder, 2022). This vaccination rate is significantly lower compared to developed countries, like the United States and China, which have single dose vaccination rates above 80% (Holder, 2022). This difference represents the insufficient distribution of COVID-19 vaccines in developing African countries.

Figure 3

Share of Each Country's Population Receiving At Least One COVID-19 Dose



Note. Adapted from Holder, J. (2022, October 1). Tracking Coronavirus Vaccinations Around the World. The New York Times. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html

While the current inequitable COVID-19 vaccine distribution is mostly attributed to the recent vaccine development and the lack of global production, it overlooks the influence of capital and infrastructure differences between developed and developing countries. Capital differences play a key role in

insufficient distribution when comparing vaccine distribution data to country income. As of June 2021, about 85% of COVID-19 vaccine doses administered have been in developed countries, while most developing countries in Africa have only administered doses to about 1% of their population (Asundi et al., 2021). However, during this time many developed countries were predicted to have a large surplus of vaccines. For example, it was estimated that the United States would have had nearly 1 billion doses in surplus at the time even if they vaccinated people over 5 years old and kept extra stockpiles (Asundi et al., 2021). In addition to capital, the lack of infrastructure has also been a driving force behind insufficient COVID-19 vaccine distribution. The main infrastructure issue revolves around production and supply chain barriers in African developing countries. Currently, Africa imports approximately 99% of vaccines administered due to a lack of manufacturing capacity (Asundi et al., 2021). In June 2021, even though "finish and fill" sites were present on the continent, there were no complete COVID-19 manufacturing chains in Africa (Asundi et al., 2021). This makes developing countries very reliant on developed countries that can produce the drug substance part of the vaccine. The lack of COVID-19 manufacturing in low-income African countries is due to technological barriers. Since the COVID-19 vaccines rely on new mRNA technology that was discovered in developed countries, the lack of trained personnel and research and design infrastructure in developing countries adds additional barriers for them to produce their vaccines (Asundi et al., 2021). Also, the lack of regulatory oversight in developing countries prevents COVID-19 vaccines from being produced due to safety concerns (Asundi et al., 2021). If only production capacity is considered responsible for insufficient COVID-19 vaccine distribution, then the actors contributing to capital and infrastructure differences will not be fully understood, and the issue of vaccine inequity will continue for developing countries. This would be problematic globally due to the

chance of new highly transmissible variants forming during COVID-19 surges in unvaccinated populations (Asundi et al., 2021).

This STS paper will analyze published research from WHO regarding the differences in COVID-19 vaccine distribution between developed and African developing countries. Additionally, research regarding the lack of capital and infrastructure in African developing countries will be reviewed to view the impact on vaccine distribution. The analysis will employ Actor-Network Theory (ANT) to explain the sociotechnical issue of vaccine inequity during the COVID-19 pandemic. The ANT approach is the idea that network actors assemble heterogeneous networks composed of human and non-human actors in order to accomplish a goal or solve a problem (Darryl Cressman, 2009). For this analysis, WHO acts as the network builder with the goal of increasing global COVID-19 vaccination coverage. ANT is especially useful for this analysis because it provides a strategy for evaluating both material and political relationships within vaccine manufacturing and distribution that WHO, the network builder, must address. Research into medical and STS literature will help define the actors involved in insufficient COVID-19 vaccine distribution in developing African countries, allowing me to understand the human and non-human actors that must be considered when distributing vaccines to developing countries. To support my argument, I will analyze evidence relating to the scope and impact of insufficient COVID-19 vaccine distribution (Asundi et al., 2021). This will provide information on how the lack of capital and infrastructure in developing African countries has contributed to insufficient vaccine distribution.

Conclusion

The deliverable for the technical problem discussed in this paper will be a cost-effective process design to manufacture the R21/Matrix-M vaccine to prevent malaria infections in

Sub-Saharan Africa. The STS research paper will aim to determine how the lack of capital and infrastructure in developing African countries has contributed to insufficient vaccine distribution. The sociotechnical analysis will be accomplished by applying Actor-Network theory to characterize how relevant human and non-human actors play a role in vaccine distribution. The combined results of this technical report will address the issues regarding access and distribution of life-saving vaccines from a sociotechnical lens, promoting an improved malaria vaccine to help eradicate a fatal parasitic disease.

Word Count: 1928

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