Prospectus

Novel Design of the RTS,S Malaria Vaccine Process Train Employing Single Use Systems
(Technical Topic)

Building a Stable Network for Vaccine Implementation in Sub-Saharan Africa
(STS Topic)

By

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October 30, 2019

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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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Socio-Technical Problem Frame:

In 2017 alone, there were 219 million cases of malaria globally, 92% of which occurred in the World Health Organization (WHO) African region (WHO, 2018). Due to the absence of effective treatment against this mosquito borne illness, malaria remains a large public health burden. Those most susceptible to infection are children under the age of five in endemic areas, who compose about two thirds of the total malaria-related fatalities each year (UNICEF Data, 2018). To make matters worse, current projections estimate that climate change will endow malaria with longer transmission periods in geographic regions beyond Africa and Asia, heightening the urgency of a long-term solution for this disease (Cho, 2019).

After 30 years of development, Pharmaceutical Group GlaxoSmithKline (GSK) released the world's first malaria vaccine, Mosquirix, in early 2019 to be administered in three African countries (Malawi, Ghana, and Kenya) as part of a pilot programme to gather efficacy and safety data. The vaccine, targeted towards young children, has so far only indicated 40% effectiveness in clinical trials over four doses, but remains a glimmer of hope for parents whose children often do not live past the age of five. Mosquirix has lost some appeal since its launch, primarily due to high retail costs that render the vaccine inaccessible to vulnerable groups (Kelland, 2015). A technical solution would reduce the cost of the first generation vaccine by optimizing its preliminary manufacturing process while still exceeding the European Medicines Agency (EMA) standards.

However, successful administration of the malaria vaccine transcends technical limitations and incorporates political, social, and economic factors. For example, in Malawi,

transportation to the clinics is inaccessible for most trial communities. This issue must be addressed via local government initiatives to improve the current infrastructure. Additionally, parents must be proactive in ensuring their kids receive all four doses of the vaccine in a timely manner to fully benefit from the efficacy of Mosquirix. As the above instances show, mere improvement of the manufacturing process is insufficient. Robust data that accurately reflects the vaccine's potency can only be compiled if state, family, and community actors all cooperate in the implementation of the malaria vaccine. This pipeline of effective vaccine administration is only stable so long as all actors involved have an interest in establishing Mosquirix. Because the programme is a new initiative, there are factors beyond the technical aspects that threaten its viability that need to be acknowledged to successfully launch the new product.

In order to address the various technical and social aspects necessary for this vaccine's effective implementation, a two-step approach is needed. First, a blueprint for an optimized manufacturing plant yielding affordable doses of the malaria vaccine that exceeds the EMA standards needs to be developed. Then, actor-network theory, specifically Michael Callon's concept of translation, will describe various human and non-human actors who make the network vulnerable at this stage.

Technical Problem Frame

In 2017 alone, malaria infections killed around 435,000 people in sub-Saharan Africa (World Health Organization, 2019a). To combat the widespread harm that malaria infections cause to populations in sub-Saharan Africa, the pharmaceutical company GlaxoSmithKline recently released an antimalarial vaccine called Mosquirix. It was approved by the European Medicines Agency (EMA) for market after being put through three phases of clinical trials

(European Medicines Agency, 2015). These rigorous trials determined its safety and efficacy in children from sub-Saharan Africa ranging in age from 6 weeks to 17 months after administration of three or four doses. Health care access in this area is inadequate because the poverty rate in sub-Saharan Africa averages 41% (Patel, 2018). The combination of the dosage requirement for this vaccine and the poverty rate in sub-Saharan Africa makes Mosquirix inaccessible in areas where it is most needed. The aim of this technical project is to modify the current manufacturing process of Mosquirix to lower the production costs and implement single use systems, while complying with the EMA standards.

The World Health Organization (WHO) has identified populations that are considerably more susceptible to contracting malaria and has begun distributing Mosquirix through the Malaria Vaccine Implementation Programme (MVIP) (World Health Organization, 2019b). Because the drug is not currently being manufactured for widespread use, the per-dose price is high. It currently costs roughly $5 to manufacture each dose (Galactionova, Bertram, Lauer, & Tediosi, 2015), including a profit margin of 5%, which is reinvested towards malaria research (Kelland, 2015). If the vaccine is to be deployed effectively, it needs to be made more affordable for the Sub-Saharan market. Without cost reduction, we will be unable to provide for the complete target population, leaving millions of lives unprotected against malaria. Our goal is to achieve production costs of $4 per dose.

The current EMA-approved continuous manufacturing process for Mosquirix begins with the fed-batch fermentation of recombinant yeast cells. The yeast cells are then harvested, disrupted, extracted, and purified using techniques such as ultrafiltration, centrifugation, and

chromatography (EMA, 2015). A generic Virus-Like Particle (VLP) production process is illustrated in Figure 1.

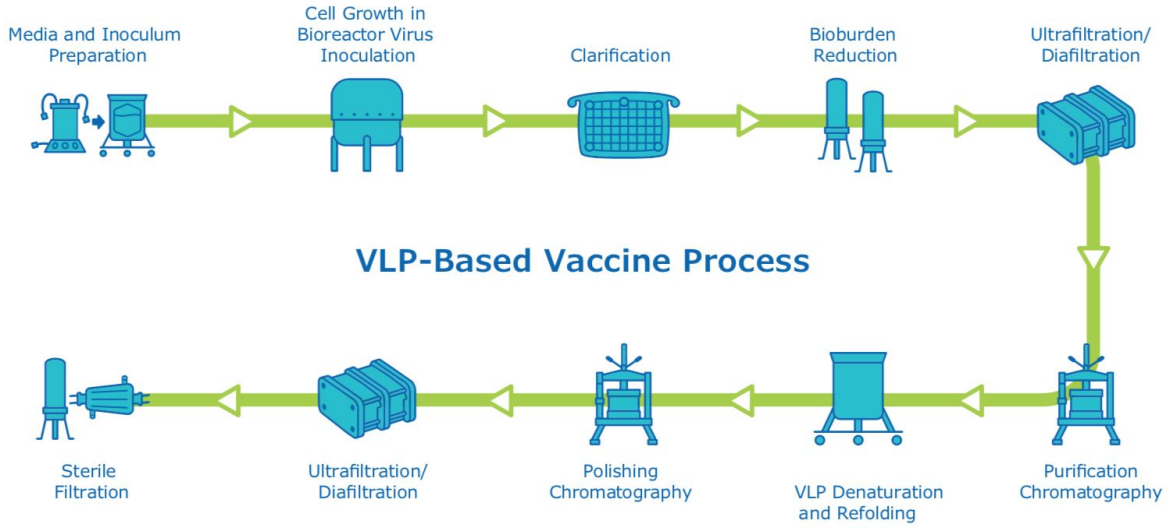

Figure 1: General Process Flow Diagram for VLP-Based Vaccine Production (EMD Millipore)

It is possible to adjust various aspects of the approved process to minimize operating costs. An increasingly popular manufacturing process involves the integration of Single-Use Systems (SUS). Pharmaceutical companies have discovered that SUS lessens overall process costs. SUS implementation can lead to lower facility footprints, smaller capital investment and construction costs, and shorter downtime of equipment resulting from reduced cleaning and sterilization times (Langer, 2018). Additional modifications to the process conditions for the manufacturing process will be considered to decrease the production cost of Mosquirix.

Literature research and data will be the primary informant of the design process, especially regarding VLP production, chromatography, single use components, and sterile filtration. We will design a media inoculum apparatus, bioreactor, clarifier, ultrafiltration and

diafiltration skid, chromatography system, and sterile filter. The project will be advised by Eric Anderson, a Professor of Practice at the University of Virginia. The team will also confer with Professors Giorgio Carta and Michael King of the University of Virginia Chemical Engineering Department. We will model the design process with simulation software such as Aspen Plus and MATLAB. Initial process parameters, such as scope and product purity, will be determined during the first semester of the academic year, while the design process will take place during the second semester. The final deliverable will be a technical report that details the fermentation and separation processes, including scale, product yield, cleaning, and scheduling. The technical report will also include an economic analysis calculating cost of startup and operation, production, sales, and research and development to ensure that our process is cheaper than the previously filed Mosquirix manufacturing process. The project will be successful if the designed process is able to produce Mosquirix in a way that is compliant with the published EMA standards and is less costly than the previously published production method.

STS Problem Frame

GSK took a leap in malaria control by introducing the malaria vaccine in Malawi, Ghana, and Kenya, as part of a pilot programme. Mosquirix could become a primary form of preventative care towards malaria if supported by the WHO. Currently, members of the Organization have maintained a neutral stance by stating they "recognize the public health potential of the… vaccine while also acknowledging the need for further evaluation before considering wide-scale deployment" (WHO, 2016). The position of WHO is subject to change depending on the results collected from the pilot programme.

Without substantial meaningful data, the WHO cannot determine the feasibility of the vaccine and its safety in the context of routine immunization, and production of Mosquirix will come to a standstill. However, there are several challenges in isolating the effects of the vaccine alone; data collection involves political, social, and economic factors as well.

Mosquirix provides partial protection against malaria in children under the age of five through a four-dose vaccine delivery schedule. The vaccine has only thus far been introduced to immunization systems in randomly selected districts within the programme, which means that not all the clinics are conveniently located and accessibility is limited. This issue is aggravated further by the underdeveloped public transportation system in certain regions, which requires support from the local government to update the current infrastructure. Additionally, studies have indicated that relational ethics, acknowledgment of community dynamics, and commitment to long-term monitoring of the implementation programme need to be prioritized to foster cooperation between researchers and trial communities for successful data collection (Berg, 2019). These are factors that may threaten the engagement of participants in the programme.

Because the cost of Mosquirix makes it inaccessible to those susceptible in endemic regions, the pilot programme has so far been able to launch due to generous donations by charities. However, the future of this funding may be unpredictable. Based on the current efficacy of the vaccine, a modest 40%, immunized children can still contract malaria. Potential distrust of patients of the WHO and sponsors makes the support of Mosquirix a reputational risk. Without open communication and robust data, GSK could face losses in financial assistance from donors (Kelland, 2015).

The success of GSK's Mosquirix greatly depends on the roles of human and non-human actors in the process of data collection. The administration of this novel vaccine by GSK can be examined by applying the science, technology, and society (STS) framework of Actor-Network Theory (ANT). ANT considers the roles of both human and non-human factors associated with a network that is designed by a network builder to achieve a common goal (Callon, 1987). To form and maintain a network, Michel Callon's concept of "Translation" can be employed, which consists of a five step method for a network builder to recruit actors: Problemitization, Interessement, Enrolment, Mobilisation, and Black-box. It is pertinent to consider the structure of the network, as technological design revolves around social and technical engineering in an environment of diverse components that must collaborate to create a stable entity (Law, 1987). The process of Translation can describe how the network that GSK, the network builder, is forming is currently vulnerable to instability.

Conclusion

Malaria will remain a public health burden until a widespread treatment method is adopted. The technical solution to this issue is to propose a production process for the newly launched vaccine, Mosquirix, that will lower the current price per dose and abide by the EMA standards in order to be accessible for all communities. A sustainable solution can only be achieved by also addressing external factors. Human and non-human actors play an important role in the creation of a stable network that allows for the evaluation of safety and efficacy of the vaccine. Actor Network Theory (ANT), specifically the concept of Translation, can describe how the current network that GSK is forming is vulnerable, which subsequently threatens the implementation of the pilot programme in sub-Saharan Africa. Considering both the technical

and STS portions of this project could lead to the prevention of hundreds of thousands of cases of malaria globally.

Word Count: 1874

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