NOVEL DESIGN OF THE RTS,S MALARIA VACCINE PROCESS TRAIN EMPLOYING SINGLE USE SYSTEMS

TECHNOLOGICAL HOMEOSTASIS OF CHILDHOOD VACCINATION IN THE UNITED STATES

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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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Since the origination of medical institutions and the first instances of inoculation, there have been tremendous strides in the advancement of medicine. The breakthroughs in vaccination made by Maurice Hilleman in the mid-20th century represent a turning point for the fields of immunology and vaccinology (Newman, 2005). The resulting prevalence and relatively inexpensive prices of common vaccines in first world countries should allow almost all members of those populations to become vaccinated. However, some populations remain or are becoming reluctant to vaccinate. This resistance to an improving technology indicates a technological homeostasis that has led to growing global health concerns. On the other hand, support for vaccination is widespread in developing countries such as sub-Saharan Africa, but the poverty rates in these countries limit the diffusivity of the technology.

According to the 2018 World Malaria Report (World Health Organization, 2019a), malaria affected 219 million people around the world in 2017. Although the number of global malaria cases dropped by 20 million between 2010 and 2017, the World Health Organization (WHO) claims that there has not been significant progress in reduction of malaria cases in recent years. To support this claim, WHO reported that the number of malaria cases decreased in Rwanda, India, Ethiopia, and Pakistan between 2016 and 2017, but countries such as Nigeria, Madagascar, and the Democratic Republic of the Congo each noticed at least 500,000 more cases in 2017 than 2016 (World Health Organization, 2018). This imbalance suggests that some countries are improving their preventative measures, through diagnostic testing, insecticidal nets, and indoor residual spraying (World Health Organization, 2019a), while others are falling behind. To assist the countries bearing the heaviest malaria burden, this technical project will focus on the construction of a functional manufacturing plant for a malaria vaccine and a water for injection (WFI) plant to supplement the vaccine production. The vaccine will be administered in sub-Saharan Africa at the lowest feasible cost to members of the target population.

Where this technical project will fail to address the sociotechnical factors of vaccine distribution, the Science, Technology, and Society (STS) paper will succeed. Specifically, the STS paper will address the educational challenges surrounding vaccination of children in technologically homeostatic societies. The antivaccination attitudes which have led to technological homeostasis will be compared between populations of sub-Saharan Africa, where the malaria vaccine will be implemented, and populations of first worlds countries such as the United States. In this way, the technical and STS papers are tightly coupled.

The members of this project include undergraduate chemical engineering students Madeline Clore, Davis Kleman, Rich Dazzo, Nushaba Rashid, and Arthur Wu. This project will be advised by Eric Anderson in the Chemical Engineering department and Catherine Baritaud in the Science Technology and Society (STS) department.

NOVEL DESIGN OF THE RTS,S MALARIA VACCINE PROCESS TRAIN EMPLOYING SINGLE USE SYSTEMS

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 for 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, 2019c). 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, including a profit margin of 5% which is reinvested towards malaria research (Galactionova, Bertram, Lauer, & Tediosi, 2015; 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. In order to reduce cost, we aim to design an efficient, large-scale production operation. Our goal is to achieve production costs of $4 per dose.

The current EMA-approved continuous manufacturing process for Mosquirix begins with 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 (European Medicines Agency, 2015). A generic Virus-Like Particle (VLP) production process is illustrated in Figure 1.

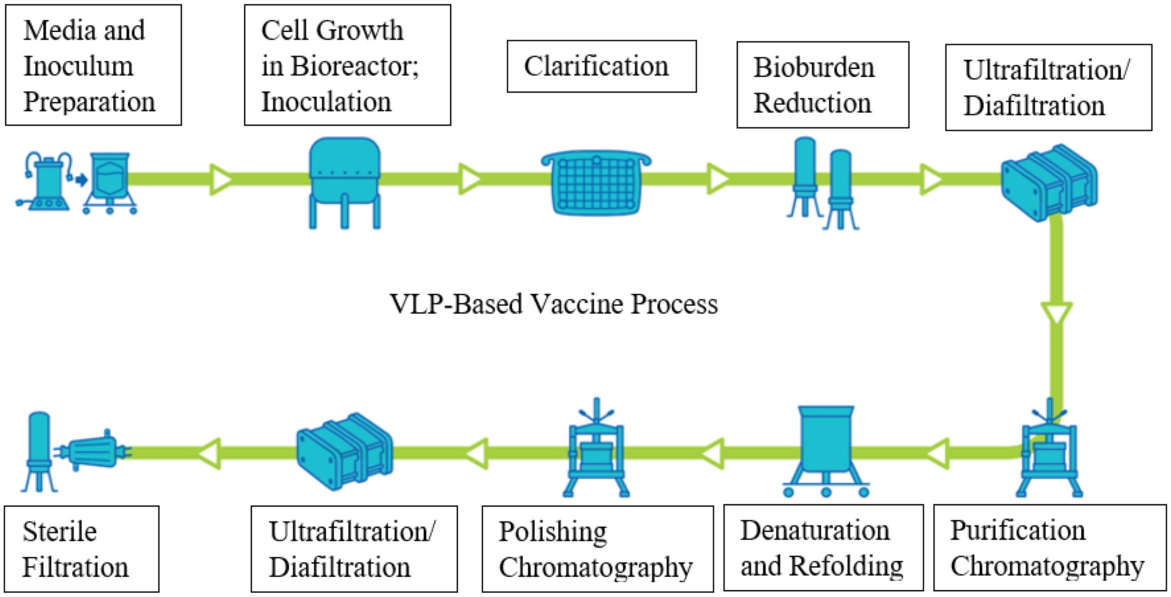

Figure 1: General Process Flow Diagram for VLP-Based Vaccine Production. (Adapted by Madeline Clore from EMD Millipore Corporation, 2016)

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 filters. 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 scalability, 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.

TECHNOLOGICAL HOMEOSTASIS OF CHILDHOOD VACCINATION IN THE UNITED STATES

Vaccine hesitancy is currently one of the top ten threats to global health (World Health Organization, 2019b). The World Health organization defines vaccine hesitancy as “the reluctance or refusal to vaccinate despite the availability of vaccines” (2019b). This reluctance has been growing around the world for decades and has been exacerbated by the ease of communication associated with the Internet. Initial records of anti-vaccination sentiments can be traced back to 1853, when the English Vaccination Act of 1853 was met with resistance. This Act made vaccination of infants mandatory, but one of its adverse consequences was the formation of the Anti-vaccination League (Kirkpatrick, 2016). Since the creation of this early set of “anti-vaxxers,” attitudes against vaccination have diffused across a broad range of countries and social groups.

Resistance to vaccination, often referred to as the “anti-vax movement,” presents a significant challenge to technological diffusion and the attainment of adequate herd immunity. Herd immunity, the concept of inoculating the greatest possible proportion of a population to prevent the spread of disease, is not successful when vaccination rates are below the critical immunity threshold (Watson, 2018). The critical immunity threshold permits a small fraction of the population to remain unvaccinated, namely the immunocompromised. Those with compromised or weakened immune systems are medically unable to safely receive vaccines, but are the primary beneficiaries of herd immunity. By refusing to vaccinate, anti-vaxxers put the immunocompromised at greater risk of disease.

A specific example of the threat that anti-vaxxers pose to public health relates to the recent measles outbreaks in the United States. As indicated by Figure 2, measles outbreaks were observed in the United States during the years 2008, 2011, 2013, 2014-2015, and 2018-2019 (CDC, 2019b; Hussain, Ali, Ahmed, & Hussain, 2018). Even without complete data for 2019, it is clear that the uptick in the number of measles cases between 2018 and 2019 is incredibly significant and

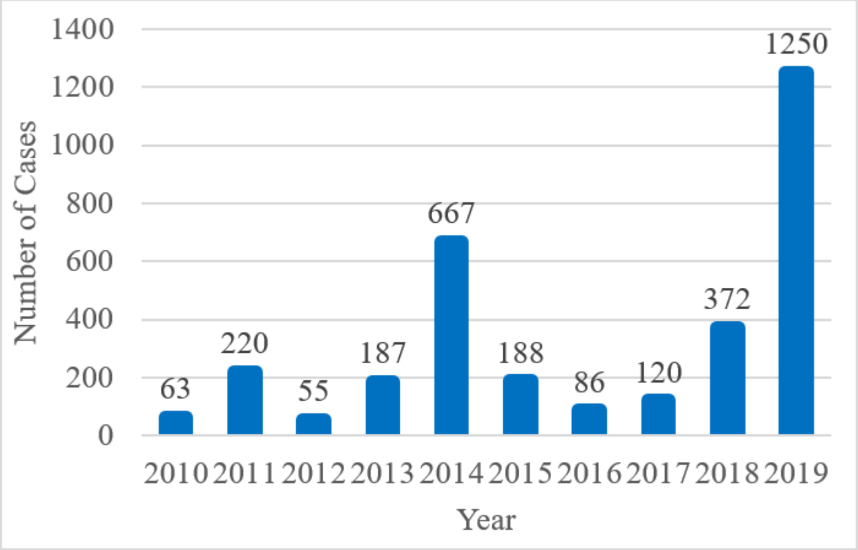

Figure 2: Number of measles cases reported to the Center for Disease Control and Prevention (CDC) between 2010 and October 3, 2019. (Adapted by Madeline Clore from CDC, 2019b)

warrants further research into the cause. As seen in Figure 3, vaccination rates for measles are not up to the 96% threshold in all states (Bowes, 2016).

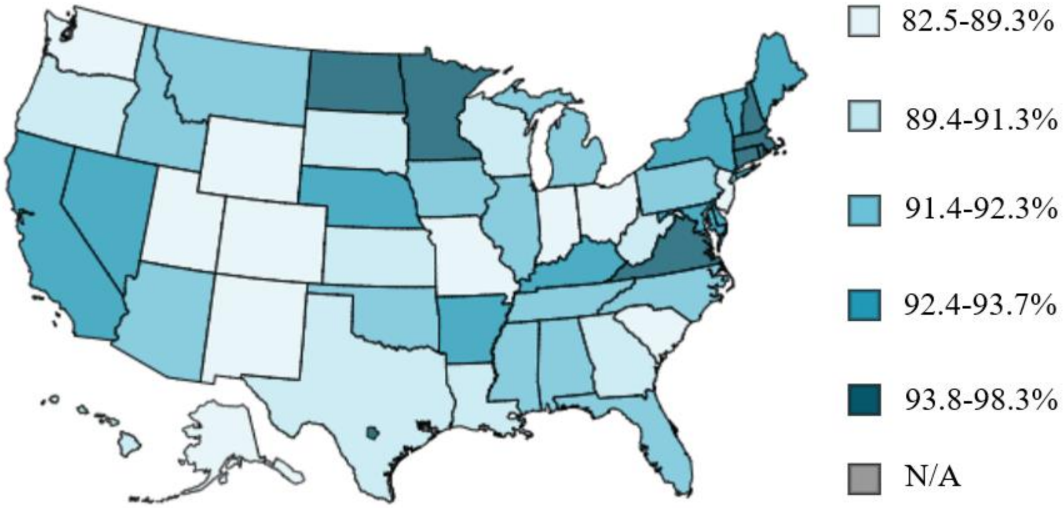

Figure 3: 2017 Measles, Mumps, and Rubella (MMR) vaccination coverage among children 19-35 months old by state (Adapted by Madeline Clore from CDC, 2019a)

These low vaccination rates suggest that herd immunity is not achieved because vaccine technology does not diffuse appropriately across the United States. While seven states have vaccination rates in the range 93.8-98.3%, only the rates in Virginia and Massachusetts exceed the 96% threshold. Their respective rates of 97.6% and 98.3% provide a case study of the effect of geographic region on vaccination rates.

THE INTERNET AS A DRIVING FORCE FOR ANTI-VACCINATION ATTITUDES

Parents who opt out of vaccinating their children often do so because they are unaware of the effect that contagious diseases can have. “Vaccines are a victim of their own success,” says Dr. Paul Offit, an expert in infectious disease at the Children’s Hospital of Philadelphia (Hoffman, 2019). By achieving reductions in the prevalence of diseases, the memory of these diseases has been eliminated. As a result, anti-vaxxers fail to see the problem that vaccines purportedly solve. This omission bias, wherein members of society would rather accept the risks associated with vaccine refusal than accept the risks of vaccination, is strongly influenced by consultation with the Internet. A prime example of the influence of the Internet concerns the Lancet study, which tied autism to the measles, mumps, and rubella (MMR) vaccine. Regardless of eventual discreditation and retraction, it instilled a fear of vaccines in populations around the world.

The Internet provides a platform for people to confirm biases and uncertainties about vaccination. Social scientist Dr. Rupali Limaye at the Johns Hopkins Bloomberg School of Public Health proposes that the widespread and constant availability of the Internet means that hesitant individuals can always consult with other anti-vaxxers (Hoffman, 2019). However, they also have the ability to read information from health organizations about the benefits of vaccination. Somehow, the unreliable sources of antivaccination material have led people around the world to reevaluate their stances on vaccination.

Individuals that engage in anti-vaccination discourse on the Internet often put strain on their patient-physician relationship; they are disengaged during or unwilling to undergo vaccine consultation (Mohanty et al., 2018). According to medical sociologist Peter Conrad, medical technologies should give health care providers the tools to “coerce others into approved, healthy lifestyles” (Timmermans & Berg, 2003). But while doctors have good reason to coerce others into receiving vaccinations, patients are not their pawns; patients must actively approve or oppose vaccinations. Anti-vax parents often undermine the expertise of their doctors; what anti-vax parents believe is medically best for their children is at odds with the opinions of their pediatricians. The resistance to authority and needs for autonomy projected by anti-vaxxers makes them difficult to educate, which in turn limits the diffusivity of the technology.

This STS paper will analyze published research regarding the vaccination rates among specific racial/ethnic groups, localities, and socioeconomic classes to address the increase in diffusion of anti-vaccination rhetoric and examine the reasons for technological homeostasis of vaccines. The analysis will employ Law and Callon's Actor-Network Theory (ANT) to explain the sociotechnical phenomenon of the anti-vax movement. Actor-Network Theory will be used in combination with Rogers's theory of Diffusion of Innovations to clarify how and why antivaccination sentiments took hold in the United States. The Actor-Network Theory approach is recommended here because there is coordination between clinical and organizational aspects of healthcare as well as two-way interactions between humans and technology (Timmermans & Berg, 2003). Actor-Network Theory is especially useful for this analysis because it provides a strategy for addressing both material and semiotic relationships.

Research into STS and medical literature will help define the actors in the anti-vax movement and describe the ways in which they interact. A schematic of the interactions between the primary actors in the anti-vax movement is illustrated in Figure 4.

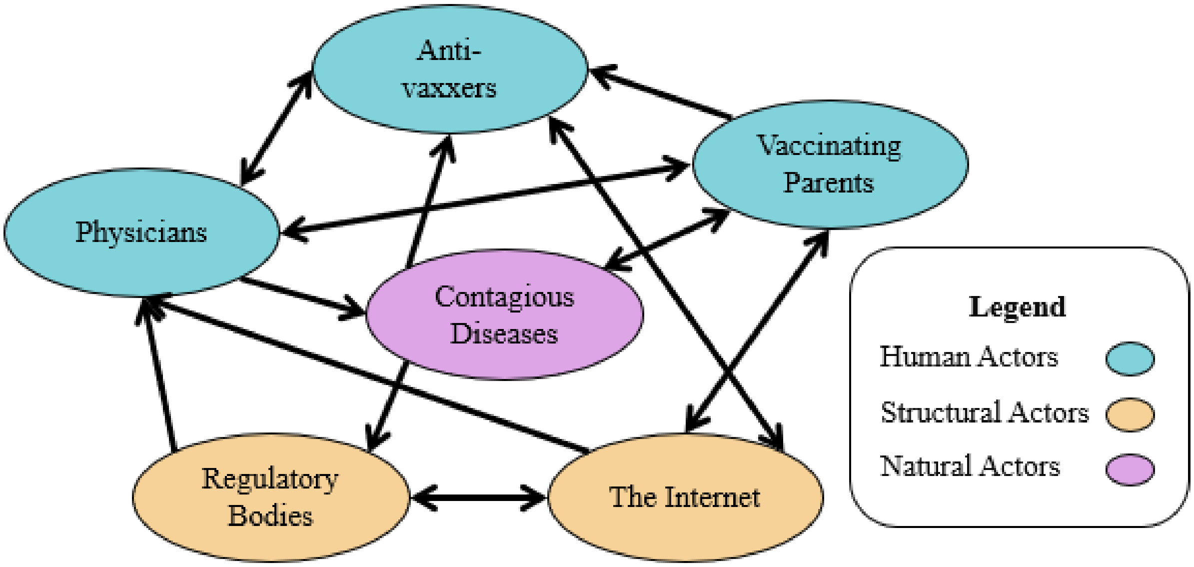

Figure 4: Primary actors in the anti-vax movement from an Actor-Network Theory perspective (Clore, 2019)

The primary actors in the anti-vax movement include anti-vaxxers, physicians, contagious diseases, the Internet, parents who vaccinate their children, and regulatory bodies. These actors interact in a broad range of ways, which can be used to explain how and why the diffusivity of vaccine technology has been hindered.

The challenges of educating anti-vaxxers that come from desires for autonomy and selective perception will be investigated in the context of social groups and disease progression to improve education of the public. The educational solution generated in the STS paper will detail the interplay of all relevant actors and will, in turn, reduce the prevalence of anti-vaccination sentiments and facilitate further diffusion of vaccine technology.

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