Novel Design of the RTS,S Malaria Vaccine Process Train Employing Single Use Systems

(Technical Paper)

Vaccines, Politics, and Logic: Why Science Failed to Quell the Antivaccination Movement

(STS Paper)

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Davis Kleman
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Technical Project Team Members
Madeline Clore
Richard Dazzo
Nushaba Rashid
Arthur Wu

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

Introduction

According to the World Health Organization, immunization through vaccination currently prevents 2-3 million deaths per year, and countless more disease contractions per year ("Immunization coverage," n.d.). Vaccines are one of the greatest inventions of humankind. However, in 2018 alone, an estimated 19.4 million children under one year of age did not receive basic vaccines. 60% of the unvaccinated children live in 10 countries, most of which are in the developing world. Two factors contributed most to this statistic: lack of access to vaccines, and refusal of parents to vaccinate their children for religious, philosophical, or political reasons. In order to widen the reach of vaccination programs, current vaccine manufacturing processes must be designed to be more affordable, so that people in developing countries can afford to buy and administer vaccines. The technical research portion of this proposal is the design of a malaria vaccine production train that produces vaccines affordable to those in sub-Saharan Africa. In order to reach those populations who are a part of the anti-vaccination movement, and refuse to vaccinate their children for one of a variety of reasons, the STS research portion of this proposal investigates the nature of the anti-vaccination movement, and provides a deeper understanding of the movement as a whole.

Technical Topic

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, 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. 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 (European Medicines Agency, 2015). A generic Virus-Like Particle (VLP) production process is illustrated in Figure 1.

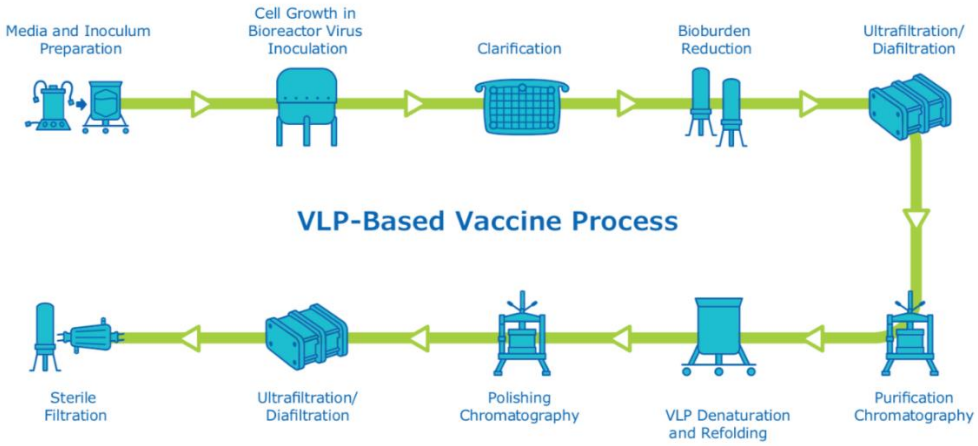

Figure 1: General Process Flow Diagram for VLP-Based Vaccine Production (EMD Millipore Corporation, 2016)

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 & Rader, 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 Topic

Healthcare worldwide was revolutionized by the invention of vaccines. Immunization by vaccination prevented at least 10 million deaths between 2010 and 2015, and millions of other lives were spared from illness (Chan, 2017). Vaccination programs also helped to almost completely eradicate diseases such as polio, rubella, and mumps in the United States. However, the use of vaccines can only help to resist the spread of a contagious disease if the immunization rate in a particular area reaches 90-95%. Otherwise, the disease is likely to spread throughout the area. This concept is called herd immunity (Carrel & Bitterman, 2015). The number of parents refusing to vaccinate their children in the United States in on the rise, thus endangering those who are unable to be vaccinated for medical reasons, and threatening herd immunity for many diseases (Carrel & Bitterman, 2015). The United States has already seen at least two outbreaks of diseases that were thought to have been almost eradicated: measles and pertussis. Both outbreaks occurred in California, and studies showed that in both outbreaks, most of those infected were not vaccinated for the diseases (Atwell et al., 2013; Zipprich et al., 2015).

Parents have resisted vaccinating themselves and their children for many different reasons in the past. Initially, the anti-vaccination movement began as a political movement: when British Parliament passed the Vaccination Act in 1853, which required that all children be vaccinated against smallpox, a group of people arose who opposed the compulsory nature of the act (Durbach, 2004). Throughout history, resistance to being vaccinated has also been for religious reasons. Many people believed, and still believe, that vaccines confiscate control of human life from God and put it into human hands (Ruijs et al., 2013). However, in 1998, the anti-vaccination argument transitioned to a pseudo-scientific one when an article was published in *The Lancet* claiming the presence of a link between the measles, mumps, and rubella (MMR) vaccine and autism (Wakefield et al., 1998). In 2010, another article was published claiming the presence of a link between the MMR vaccine and autism in young African American boys (Hooker, 2014). The results of people not vaccinating the children could clearly be seen when in February 2015, the CDC published a Morbidity and Mortality Weekly Report detailing a measles outbreak that occurred in California from December 2014 to February 2015 (Zipprich et al., 2015). The report claimed that 45% of cases were confirmed unvaccinated, while 43% had unknown or undocumented vaccination status.

Since the anti-vaccination movement has been present since the inception of vaccines themselves, the reasons for vaccine opposition have also changed over time, from political to religious to pseudo-scientific. In order to fully understand the antivaccination movement, reasons to not vaccinate must be investigated and thoroughly analyzed. In this STS Thesis research paper, I intend to investigate the extent to which the papers published claiming a link between the MMR vaccine and autism, and subsequent scientific papers contradicting that claim, affected the anti-vaccination movement as a whole. I will determine whether the papers persuaded many

people to oppose vaccines, and if the literature that followed disproving the link between autism and vaccines actually lessened the effect of the movement. If many people are against vaccines for reasons other than the pseudo-scientific, then the papers claiming the link between autism and vaccines, and the papers disproving that link, would not have affected the movement greatly. I write this thesis with the hope that subsequent papers will be written detailing the other reasons parents choose to not vaccinate, so that the anti-vaccination movement may be fully understood, and subsequently put to rest.

Two sociotechnical frameworks will be used to investigate the impact of the autism papers on the antivaccination movement as a whole, one of which is the Political Technologies framework, explored by Langdon Winner in "Do Artifacts have Politics?" In his paper, Winner outlines two ways artifacts can have politics, or give someone power and authority. Some objects have politics when certain aspects of the design of a device or system are able to provide power or authority, while other objects can have politics if they are designed with the explicit purpose of giving an entity power or authority (Weckert, 2017). I intend on using the Political Technologies framework to show that vaccines are able to provide power to governments or other institutions in some instances. The second sociotechnical framework used in this STS thesis is the Technological Fix, outlined by Byron Newberry in his encyclopedia entry, "Technological Fix." In his entry, Newberry defines the technological fix as "the use of technology to respond to certain types of human social problems that are more traditionally addressed via political, legal, organizational, or other social processes" (Mitcham, 2005). I intend on using the Technological Fix framework to show that the many papers published showing that vaccines do not cause autism may have not been the most effective method in persuading people of the safety of vaccines.

Research Question and Methods

The question that will be investigated in this research paper is: How did the literature published claiming the existence of a link between vaccines and autism, and the literature disproving that claim, affect the anti-vaccination movement as a whole? This question will be investigated primarily through documentary research and discourse analysis, as many of the opinions on vaccination people have expressed has already been captured in prior work on the vaccination movement. I will use two articles reporting disease outbreaks and personal vaccine exemptions in California (Atwell et al., 2013; Zipprich et al., 2015) to provide background on the consequences of not being vaccinated, and to show how relevant the issue is. I will use two papers claiming the existence of a link between vaccines and autism (Hooker, 2014; Wakefield et al., 1998) and an array of papers disproving that claim (DeStefano, 2007; Miller & Reynolds, 2009; Plotkin, Gerber, & Offit, 2009; Stehr-Green, Tull, Stellfeld, Mortenson, & Simpson, 2003; Taylor, Swerdfeger, & Eslick, 2014) to provide a background of what may have affected the movement. I will use a book about the anti-vaccination movement in England (Durbach, 2004) to detail the beginnings of the movement, and why people initially were against vaccination. I also plan on using research papers to determine the reasons why modern people are choosing not to vaccinate the children, whether they are political, religious, or philosophical (Carrel & Bitterman, 2015; Ruijs et al., 2013). Hopefully by delving into why people are against vaccination I can discover the overall effects of the autism papers, and whether they actually swayed peoples' opinions on vaccines. The research for this paper will be completed midway through the second semester of the 2019-2020 school year, and the paper itself will be completed by the end of the academic year.

Conclusion

The two deliverables to be completed will both hopefully advance efforts to achieve complete worldwide vaccination coverage. The technical deliverable, a design of a malaria vaccine production train, will hopefully produce vaccines affordable to those in southern Africa will provide greater accessibility to a lifesaving vaccine. I anticipate that the train will be able to produce a malaria vaccine that is less expensive than the vaccine produced by GlaxoSmithKline. The STS deliverable, a paper about the effect of literature claiming a link between autism and vaccination, will attempt to provide a deeper understanding of the movement as a whole. I would like to show that the anti-vaccination movement is not a monolith of people that believe that vaccines cause autism, rather a group of people with a very diverse set of beliefs. I believe that in writing the STS deliverable, I will find that the reasons that parents use to avoid having their children vaccinated to be so diverse that the papers linking vaccines to autism had a negligible effect on the movement, and therefore the massive amounts of effort dedicated to disprove those papers are misplaced.

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