Prospectus

COVID-19 Vaccine Production Process with a Baculovirus Expression Vector System
(Technical Topic)

Anti-Vaccination Movement in the United States
(STS Topic)

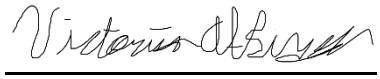
By

Victoria Atkinson

11/23/2021

Technical Project Team Members: Gordon Lee, Grant Martin, Anthony Ouertani, Derek 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.

Signed: 

Approved: _____ Date _____
Ben Laugelli, Department of Engineering and Society

Approved: _____ Date _____
Eric Anderson, Department of Chemical Engineering

Introduction

Coronavirus disease 2019 (COVID-19), the highly contagious infectious disease caused by the novel SARS-CoV-2 virus, remains a major global health concern. To date, there have been over 240 million confirmed cases and 4.8 million deaths worldwide ("WHO COVID-19 Dashboard"). Nevertheless, 6 billion doses of vaccines have been administered, with many well-developed nations, including the United States, UK, and members of the EU, having vaccination rates that exceed 50% ("WHO Coronavirus Dashboard"; Mwai, 2021). However, only 2.5% of people in low-income countries have received at least one vaccine dose (Ritchie et al., 2020). Furthermore, 50 countries have not met the 10% vaccination target set by the World Health Organization (WHO) for the end of September 2021 (Mwai, 2021). A majority of these countries are located in Africa, where the overall vaccination rate is less than 5% (Mwai, 2021). More people all over the world need to be vaccinated to stop the spread of this virus.

To reach a target of 70% vaccination worldwide, an estimated 11 billion doses are required. COVAX, an organization co-led by CEPI, Gavi, and WHO, aims to donate enough vaccine doses to vaccinate 20% of low-middle income countries (WHO). By vaccinating 20% of low-middle income countries, health care workers and high-risk citizens can acquire protective immunity against COVID-19. However, a low supply of vaccines has prevented COVAX from reaching their initial goal (Paton & Bloomberg, 2021). More vaccine doses are sorely needed. Many of the vaccines currently being administered require extremely cold storage. Therefore, my team's project plans to use the baculovirus expression vector system to produce the vaccines enabling them to be stored at normal refrigeration temperatures (Sagonowsky, 2020). The ultimate goal of the technical project is to design a rapid, safe, and cost-effective production

process for a recombinant spike protein-based SARS-CoV-2 vaccine using the baculovirus expression vector system.

While the vaccine certainly is the best way to prevent the spread of coronavirus, it will not end the COVID-19 pandemic. Creating a vaccine does not address the non-technical social and political issues surrounding vaccination. These non-technical factors include misinformed safety concerns, political beliefs, and social media that cultivate opposition to vaccines. Therefore, the STS Project will be used to gain a better understanding of the actors contributing to the anti-vaccination movement surrounding the measles, mumps, and rubella (MMR) vaccine. This movement destabilized the vaccination network which resulted in the 2019 measles outbreak. If both the technical and non-technical problems are not addressed, then herd-immunity will not be reached, and the pandemic will persist leading to more disease outbreaks.

To effectively end the COVID-19 pandemic, the technical problem and social issues must be addressed concurrently. I will address this problem by developing the technical specifications for a chemical engineering pharmaceutical plant to produce the COVID-19 vaccines. I will also study the 2019 measles outbreak to determine what human and non-human actors contributed to the persistence of the anti-vaccination movement.

Technical Project

COVID-19 vaccines currently on the market notably include Pfizer-BioNTech's and Moderna's mRNA-based vaccines. Although these vaccines have efficacies over 90%, they present a problem to supply chains in their requirement for extremely cold storage: between -50°C and -15°C for Moderna and between -90°C and -60°C for Pfizer (CDC, 2021). This frozen storage is not an issue for developed countries that have the resources and infrastructures to accommodate a low temperature-controlled supply chain. However, it is an issue for the 3 billion

people in locations where cold chain storage is not easily accessible (Hinnant, 2020). Currently, Sanofi and GSK are developing a recombinant protein vaccine in phase 3 clinical trials with 95% efficacy after the 2nd dose (Sanofi, 2021). This vaccine is manufactured using the baculovirus expression vector system and can be stored at normal refrigeration temperatures, providing considerable potential for low-income nations (Sagonowsky, 2020).

Baculoviruses are a family of viruses that are known to infect insects. The baculovirus expression vector system (BEVS) is an important biotechnology tool because it can be used to insert protein-coding DNA into insect cells (Felberbaum, 2015). Once infected, the insect cells are instructed to reliably produce the antigen protein which, when inserted in the human body, initiates an immune response, producing antibodies that protects against future infection. A key feature of BEVS is its flexibility to be engineered with features that can increase product immunogenicity and facilitate purification (Deschuyteneer, 2010; Chen et al., 2013). Additionally, products made from BEVS are free of pathogens, proteins, and other chemicals that can be undesirable or allergenic (Caubet, 2014). The BEVS platform also has safety features built-in. Baculoviruses are very selective in their choice of hosts to infect; they cannot infect mammals, plants, fish, or non-target insects (Hu, 2005). Unlike many other vaccine production processes, BEVS does not require handling of live, potentially-dangerous pathogens, reducing the biocontainment requirements (Felberbaum, 2015). Compared to other biopharmaceutical manufacturing platforms, such as those used in the production of mRNA- and viral vector-based vaccines, BEVS is associated with lower manufacturing costs and easier scalability. Insect cells are grown in suspension and are only limited by the size of the bioreactor (Felberbaum, 2015). As such, utilizing the existing global bioreactor capacity can reduce initial investment costs for BEVS facilities (Felberbaum, 2015). These facilities can manufacture multiple types of vaccines

using the same cell line and equipment (Josefsberg, 2012). Furthermore, genetic and fermentation-based approaches exist that are known to improve product yield (Cox, 2012). There are currently four BEVS-derived products approved for human use including the Flublok® vaccine for seasonal influenza and the Cervarix® vaccine to prevent certain types of cancer-causing human papillomavirus (HPV). For these reasons, BEVS is an appealing option for the manufacture of a high-efficacy COVID-19 vaccine.

The goal of this project is to design a rapid, safe, and cost-effective production process for a recombinant spike protein-based SARS-CoV-2 vaccine using the baculovirus expression vector system. Thirty-six percent of the global population is fully vaccinated, and there are 22 authorized vaccines in use currently (Zimmer et al., 2020). In order to provide enough vaccines for the rest of the population, this process will be designed to produce 400 million vaccine doses per year. The process will be divided into upstream and downstream processing and will be modelled at the industrial scale for mass production of a single-use injectable. Upstream processing will include a multistep seed train, in which *Spodoptera frugiperda* (Sf9) insect cells will be grown from a master cell bank and scaled up from flasks to bioreactors. Cell growth kinetic data will be obtained from a study by Rhiel et al. (1997). A similar scale-up procedure will be used to amplify the recombinant baculovirus in inoculated insect cells and produce the desired active pharmaceutical ingredient (API). Downstream processing will include a series of unit operations to recover, purify, and formulate the bulk API. Membrane filtration, namely diafiltration and virus filtration, will be performed to remove cell debris and concentrate the target spike protein. To selectively isolate the protein of interest, affinity chromatography and ion-exchange chromatography will be conducted, since this combination of chromatography techniques is common in literature (O'Shaughnessy & Doyle, 2011). A viral inactivation step

will be performed to prevent viral contamination of the API. In the final formulation stage, the API will be combined in aqueous solution with adjuvant, stabilizers, and preservatives. The vaccine will be formulated with the Adjuvant System 03 (ASO3) manufactured by GlaxoSmithKline (GSK), which reduces the amount of API needed by enhancing the immune response. Finally, the product will be filled into single-use vials with 10 µg of the API. Since each stage of this process must be performed in a sterile environment, a reverse osmosis based system to produce Water For Injection (WFI) will be designed. Sequencing of the spike protein gene and the genetic modification of the baculovirus are beyond the scope of this project.

The technical design team will investigate the COVID-19 vaccine production process during the fall and spring semesters in CHE4474 and CHE4476, respectively. The team will meet weekly to review the progress on the project and assign tasks for the following week. Additionally, the team will meet periodically with our faculty advisor, Prof. Eric Anderson, to receive feedback and guidance as the project progresses. Throughout the technical project design, the team will rely on the expertise from the University of Virginia's Chemical Engineering department faculty: Professor Michael King, an industry expert on vaccine production, and Professor Giorgio Carta, who is very experienced with the downstream bioseparation process. Relevant data will be gathered from prior research on the COVID-19 vaccine and other vaccines manufactured using BEVS to inform the technical design. We will also draw insight from clinical trial data for the Sanofi-GSK BEVS COVID-19 vaccine.

STS Project

In 2000, measles, a highly contagious viral illness, was declared eliminated from the United States by the CDC thanks to the MMR vaccine (CDC, 2020). However, in 2019, unvaccinated travelers caught the disease visiting other countries and brought it back into the United States.

This led to a large measles outbreak that included a total of 704 cases during January 1-April 26, 2019; 71% of patients were unvaccinated (Patel et al., 2019). Articles published by former British doctor Andrew Wakefield in 1998 and the movie *Vaxxed* in 2016 (falsely) suggested links between the MMR vaccine and autism in young children (Benecke & DeYoung, 2019; Broniatowski et al., 2020). This led to misinformed safety concerns surrounding the MMR vaccine that fueled the anti-vaccination movement. Pro-vaccination groups, medical professionals, and government officials tried to counteract the spread of misinformation about the MMR vaccine.

While the spread of this misinformation largely contributed to the negative sentiments surrounding the MMR vaccine, it overlooks the influence of social media and the rise of vaccines as a political issue. Social media plays a pivotal role in the spread of misinformation, as it exposes billions of users to vaccine misinformation and fear-based messaging. Additionally, vaccines have become a political debate as people argue that mandatory vaccinations infringe on their liberty. If only the safety and efficacy concerns are considered responsible for persistence of the anti-vaccination effort, then we will not fully understand the influence of these other crucial actors, and more outbreaks within unvaccinated communities may develop in the future.

Drawing on Actor Network Theory (ANT), I argue that misinformation in conjunction with political beliefs are fueled by social media resulting in the persistence of the anti-vaccination movement. These actors were especially problematic to the MMR vaccination network because they sparked distrust in medical professionals and civil liberties issues that led to vaccine opposition. These unvaccinated communities are then susceptible to disease outbreaks. Actor network theory is a constructive framework in which the engineer is a network builder that assembles non-human and human actors to form a network (Cressman, 2009). ANT will allow

me to analyze how the MMR vaccination network was created and maintained, and how the rogue actors involved in the anti-vaccination movement destabilized this network. This will allow me to gain an understanding of the human and non-human actors that must be accounted for to prevent future disease outbreaks. To support my argument, I will analyze evidence from the 2019 measles outbreak by reviewing social media posts and vaccination information from medical professionals (Hoffman, 2019). This will provide information about how social media fueled political debate surrounding the MMR vaccine.

Conclusion

The ultimate goal of the technical project is to design a rapid, safe, and cost-effective production process for a recombinant spike protein-based SARS-CoV-2 vaccine using the baculovirus expression vector system. This vaccine will provide protection against the COVID-19 virus. The STS project will use Actor Network Theory to analyze how social media fueled political debate and misinformation surrounding the MMR vaccine leading to the 2019 measles outbreak. This STS research will be used to combat the anti-vaccination movement as it pertains to the COVID-19 vaccine today. Together, the technical project and the STS project will provide a greater understanding on how create an effective vaccine and persuade anti-vaccination groups to get vaccinated in order to end the COVID-19 pandemic.

Word Count: *1991*

References

Benecke, O., & DeYoung, S. E. (2019). Anti-Vaccine Decision-Making and Measles Resurgence in the United States. *Global pediatric health*, 6. doi: 10.1177/2333794X19862949

Broniatowski, D. A., et al. (2020). Facebook pages, the "Disneyland" measles outbreak, and promotion of vaccine refusal as a civil right, 2009–2019. *American Journal of Public Health*, 110(S3), S312-S318. https://doi.org/10.2105/AJPH.2020.305869

Caubet, J.C., & Ponvert, C. (2014). Vaccine allergy. *Immunol. Allergy Clin. of North Am*, *34*(3), 597– 613, ix. doi: 10.1016/j.iac.2014.04.004

Chen, C. Y., Lin, S. Y., Cheng, M. C., Tsai, C. P., et al. (2013). Baculovirus vector as an avian influenza vaccine: Hemagglutinin expression and presentation augment the vaccine immunogenicity. *J Biotechnol.*, *164*(1), 143-150. doi: 10.1016/j.jbiotec.2012.12.013

COVAX. (n.d.). World Health Organization. Retrieved October 14, 2021, from https://www.who.int/initiatives/act-accelerator/covax.

Cox, M.M.J. (2012). Recombinant protein vaccines produced in insect cells. *Vaccine*, *30*(10), 1759-1766. doi: 10.1016/j.vaccine.2012.01.016

Cressman, D. (2009). A brief overview of actor-network theory: Punctualization, Heterogeneous Engineering & Translation. Center for Policy Research on Science & Technology. Retrieved from https://summit.sfu.ca/item/13593

Deschuyteneer, M., Elouahabi, A., Plainchamp, D., Plisnier, M., et al. (2010). Molecular and structural characterization of the L1 virus-like particles that are used as vaccine antigens in Cervarix, the AS04-adjuvanted HPV-16 and -18 cervical cancer vaccine. *Hum. Vaccin*, 6(5), 407– 419. DOI: 10.4161/hv.6.5.11023

Felberbaum, R.S. (2015). The baculovirus expression vector system: A commercial manufacturing platform for viral vaccines and gene therapy vectors. *Biotechnology journal*, *10*(5), 702-714. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159335/

Hinnant, L. (2020, October 19). Vaccine storage issues could leave 3B people without access. AP NEWS. Retrieved October 14, 2021, from https://apnews.com/article/virus-outbreak-pandemics-immunizations-epidemics-united-nations-fc4c536d62c5ef25152884adb1c14168.

Hoffman, B.L., et al. (2019) It's not all about autism: The emerging landscape of anti-vaccination sentiment on Facebook. *Vaccine*, *37*(16), 2216-2223. DOI: https://doi.org/10.1016/j.vaccine.2019.03.003.

Hu, Y.C. (2005). Baculovirus as a highly efficient expression vector in insect and mammalian cells. *Acta Pharmacol. Sin.*, *26*(4), 405– 416. doi: 10.1111/j.1745-7254.2005.00078.x

Josefsberg, J.O., & Buckland, B. (2012). Vaccine process technology. *Biotechnol. Bioeng.*, *109*(6), 1443-1460. doi: 10.1002/bit.24493

Measles: Answers to Common Questions. (2020, November 5). Centers for Disease Control and Prevention. Retrieved October 23, 2021, from https://www.cdc.gov/measles/about/faqs.html

Moderna Covid-19 Vaccine. (2021, August 24). CDC. Retrieved October 14, 2021, from https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/storage-summary.pdf.

Mwai, P. (2021, October 1). Covid-19 vaccinations: More than 50 nations have missed a target set by the WHO. BBC News. Retrieved October 14, 2021, from https://www.bbc.com/news/56100076.

O'Shaughnessy L., Doyle S. (2011). Purification of Proteins from Baculovirus-Infected Insect Cells. In: Walls D., Loughran S. (eds) Protein Chromatography. *Methods in Molecular Biology (Methods and Protocols)*, vol 681. Humana Press. https://doi.org/10.1007/978-1-60761-913-0_16.

Patel M, Lee AD, Redd SB, et al. Increase in Measles Cases — United States, January 1–April 26, 2019. *Morbidity and Mortality Weekly Report.* 2019; 68:402–404. DOI: http://dx.doi.org/10.15585/mmwr.mm6817e1

Paton, J., & Bloomberg. (2021, September 8). Global covid vaccine program covax falls short of its distribution target. *Fortune*. Retrieved October 14, 2021, from https://fortune.com/2021/09/08/covax-global-vaccine-program-low-income-countries/.

Pfizer-biontech COVID-19 vaccine. (n.d.). CDC. Retrieved October 14, 2021, from https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/downloads/storage-summary.pdf.

Rhiel, M., Mitchell-Logean, C. M., & Murhammer, D. W. (1997). Comparison of Trichoplusia ni BTI-Tn-5B1-4 (high five) and Spodoptera frugiperda Sf-9 insect cell line metabolism in suspension cultures. *Biotechnology and bioengineering*, *55*(6), 909–920. https://doi.org/10.1002/(SICI)1097-0290(19970920)55:6.

Ritchie, H., Mathieu, E., Rodés-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., Hasell, J., Macdonald, B., Beltekian, D., & Roser, M. (2020, March 5). *Coronavirus (COVID-19) vaccinations - statistics and research*. *Our World in Data*. Retrieved October 17, 2021, from https://ourworldindata.org/covid-vaccinations.

Sagonowsky, E. (2020, November 11). Pfizer's COVID-19 vaccine looks impressive, but Sanofi, J&J and Novavax shots eye a logistics edge. *FiercePharma*. Retrieved October 14, 2021,

from https://www.fiercepharma.com/pharma/despite-pfizer-s-high-efficacy-expectations-other-covid-vaccines-may-have-a-logistics-edge.

The Adjuvanted Recombinant Protein-based Vaccine candidate. (n.d.). Sanofi. https://www.sanofi.com/en/our-covid-19-vaccine-candidates/recombinant-vaccine.

WHO coronavirus (COVID-19) dashboard. (n.d.). World Health Organization. Retrieved October 14, 2021, from https://covid19.who.int/.

Zimmer, C., Corum, J., & Wee, S.-lee. (2020, June 10). *Coronavirus vaccine tracker*. The New York Times. Retrieved October 12, 2021, from https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html#novavax.