**Industrial-Scale Manufacture of a Recombinant Protein-Based COVID-19 Vaccine**
(Technical Topic)

**The Politics Fueling Global Vaccine Distribution Inequality**
(STS Topic)

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By
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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

Since the World Health Organization declared the Coronavirus disease 2019 (COVID-19) a pandemic in March 2020, a global public health effort has been mobilized to vaccinate the world population against the highly contagious disease (WHO, 2020). Despite the rapid development of several effective vaccines, a majority of these vaccines have been secured by high-income countries for domestic use, leaving low-income nations with vaccination rates below 3% as 2021 draws near to a close (WHO, 2020). Inequities in global vaccination campaigns have been a prominent feature of pandemics since mass immunization originated at the end of the 18th century with the development of the first smallpox vaccine ("A brief history," 2020). Although there is an urgent need to produce more vaccines in order to reach the estimated herd immunity threshold of at least 70% of the global population, this goal can only be attained by adopting a more equitable approach to global vaccine provision (Randolph & Barreiro, 2020). For this reason, my chemical engineering Capstone team aims to contribute to the global vaccine supply by designing an industrial-scale process for the production of a SARS-CoV-2 spike protein vaccine using a reliable and well-studied manufacturing platform. Tightly coupled to this technical project, my STS research paper seeks to investigate the politics underpinning mass vaccination campaigns, particularly in the contexts of the 19th and 20th century efforts that culminated in the successful eradication of smallpox and of the ongoing COVID-19 pandemic, that perpetuate inequalities in global vaccine distribution.

## Technical Topic

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). 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.

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 administered to 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 to the vaccine. Finally, the drug 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, Professor 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 Topic

In April 2021, the Director-General of the World Health Organization (WHO) declared to a special ministerial meeting of the United Nations Economic and Social Council (ECOSOC) that "vaccine equity is the challenge of our time," alluding to the staggering inequalities in the global distribution of the COVID-19 vaccine (United Nations, 2021). At the time of this statement, 1 in 4 people had been vaccinated against the coronavirus in high-income economies compared to only 1 in 500 in low-income countries, concentrated predominately in Africa, Asia, and Latin America (United Nations, 2021). Nearly a year after the initial stages of vaccine rollout, the gap between available vaccines and vaccinated people remains vast. The privileging of wealthy countries in vaccine allocation is not a new phenomenon; it is a historical trend that

has defined past pandemics from the 1918 Spanish Flu (Murray et al., 2006) to more recent threats, such as Ebola and Zika (Hoffman & Silverberg, 2018).

Vaccines are complicated technologies that raise political questions such as who is responsible for purchasing them, what types of vaccines will be used, and who exerts control over their quality and usage. Therefore, a mass vaccination campaign is an ideal lens through which to view Langdon Winner's Theory of Technological Politics (1980). This theory is predicated on the argument that technological creations – be it agricultural tools, military arms, or transportation systems – are more than just neutral instruments that humans can use as means to an end. Winner differentiates his theory from other theories on the social construction of technology (SCOT) by proposing that technologies have political properties and embody forms of authority and subordination (1980). Within this framework, politics refers to arrangements of power and authority in human affairs as well as to the activities that occur within these arrangements (Winner, 1980). To answer the question he poses as the title of his essay – "do artifacts have politics?" – Winner identifies two ways in which technologies can have politics. The first interpretation concerns how flexibility in the design and arrangement of a technical device or system can make these technologies a convenient mechanism for establishing patterns of power and authority in a particular community. The second perspective pertains to technologies that are "inherently political" by virtue of either their requirement for or strong compatibility with specific forms of political relationships.

I will use Langdon Winner's Theory of Technological Politics (1980) to argue that mass vaccination campaigns have political qualities and require the creation and maintenance of certain social structures for their implementation. These social structures will be discussed in the contexts of national sovereignty, geopolitical strategy, and intellectual property (IP) regimes. This analysis will lead to the claim that domestic policy agendas shape the international vaccine supply chain and thereby perpetuate inequities in global vaccine provision. In their collection of essays, Holmberg et al. (2017) draw on Winner's Theory to investigate the political dimensions of vaccination strategies at different times in different parts of the world and under different types of political regime. Of particular value in this work is a rigorous analysis of the 19$^{th}$ and 20$^{th}$ century smallpox vaccination efforts that began with English doctor Edward Jenner's pioneering of the world's first vaccine and culminated in the successful eradication of the disease

in 1977 ("History of smallpox," 2021). I intend to recast Holmberg et al.'s smallpox analysis as a framework to help situate the COVID-19 pandemic in a long history of politically-shaped vaccination campaigns. I have decided to limit my focus to the smallpox and COVID-19 immunization programs because they represent the chronological extremes of humanity's fight against communicable diseases using vaccines. Furthermore, I would like to understand if changes in vaccine politics that have occurred within the last 20 years – such as the growing concern about vaccine safety and the establishment of new initiatives like the Vaccine Independence Initiative (VII) and the Global Alliance for Vaccines and Immunization (Gavi) aimed at increasing access to immunization in low-income countries – have had an appreciable impact on the way vaccination programs are designed.

Many studies on vaccine politics suggest that vaccines are inherently political due to their requirement for centralized control. Some scholars like Holmberg et al. are unambiguous in their characterization of vaccination campaigns as "expressions of state power" (2017, p.1). By likening vaccines to taxation and conscription programs, this research highlights the conditions that entangle vaccines in controversy, inspiring civic duty and shared solidarity in some social groups and vehement opposition in others. Researcher Dian Woodle suggests that vaccination programs naturally gravitate towards centralized, hierarchical arrangements of management in order to avoid the inefficiencies in scarce resource expenditure, disease surveillance, and drug storage and distribution that are associated with decentralization (2000). A prominent theme present in the existing literature on the topic of vaccine politics is the role vaccines play in building and sustaining national sovereignty. One group of historians focuses on the acquisition of national sovereignty by middle- and low-income countries through movements towards self-sufficiency in vaccine manufacture and procurement (Blume & Zanders, 2006; Muraskin, 2004). These historians are interested in the incentives that compel developing countries to set aside their local health needs and instead align with global priorities. Other scholars approach the issue of sovereignty from the perspective of high-income countries, which allows for a discussion on how vaccines cultivate nationalistic sentiment and fuel competition between nations (Fidler, 2020; Katz et al., 2017). In this context, national vaccination is a game in which victory can be purchased by the countries with the economic means to afford it. Although wealthy nations should have a critical interest in assisting global vaccination in order to minimize the damage to healthcare systems and economies, inequalities persist due to a fundamentally flawed view of

global health, in which vaccines and essential medications are treated as profitable commodities rather than guaranteed public goods (Katz et al., 2021). There is also an abundance of literature on vaccine diplomacy. Countries with a monopoly on production capacity wield vaccines as a diplomatic instrument to reconfigure geopolitical arrangements to their advantage. For example, China has withheld its COVID-19 vaccine supply from Taiwan in an effort to further isolate the island (Pratt & Levin, 2021).

This research is valuable because it demonstrates how vaccines are similar to legislative acts and other expressions of state power that establish a framework for an enduring public order. By exposing the political implications of vaccines and the ways in which history continues to repeat itself, this research will allow the reader to gain insight into how vaccination campaigns can be made a more equitable and sustainable solution to halting the spread of communicable diseases.

## Next Steps

In the short term, my Capstone team will produce a design basis memorandum to define fundamental design parameters for our vaccine production process. This document will include a description of all raw materials and products (formulation, purity, and production scale), mass and energy balances, chemical reactions and kinetics data, and a simple economic analysis to determine if the vaccine product is profitable. I will begin my STS paper by identifying the relevant stakeholders – the haves and have-nots – in order to establish that vaccine distribution inequality is a legitimate, systemic problem for global vaccination programs. A majority of my STS paper's supporting evidence on the origins of vaccination as a politicized public health measure will be drawn from Holmberg et al.'s collection of essays (2017) on the history of politics in mass vaccination campaigns. Within the next few months, I will read sections of this text that are relevant to my research. I will leverage this text's analysis of the smallpox global vaccination program as a blueprint to interrogate the political conditions that have impeded the progress of COVID-19 vaccination efforts. Both the technical Capstone project and the STS research paper will be completed by May 2022.

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