PRODUCTION OF A RECOMBINANT SPIKE PROTEIN-BASED SARS-COV-2 VACCINE USING THE BACULOVIRUS EXPRESSION VECTOR SYSTEM

A UTILITARIAN ETHCIAL FRAMEWORK FOR THE DISTRIBUTION OF VACCINES AND BOOSTER SHOTS

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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

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, 2021a). 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 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, 2021b). 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). Our technical project will be the design of a facility to manufacture doses of the Sanofi and GSK vaccine. Later, I will focus on the United States', Russia's, and China's public policy decisions towards distribution of the vaccines they produce using the utilitarian ethical framework.

Design of a Vaccine Manufacturing Facility for a Recombinant SARS-CoV-2 Vaccine

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.

A Utilitarian Ethical Framework to Combat a Syndemic

The idea of a "syndemic" instead of a pandemic has been coined in recent decades. A syndemic is defined as the combination of social, economic, and political factors that all contribute to a health crisis (Jecker et. al, 2021c). Diseases do not exist by themselves in a vacuum. Social conditions such as poverty, overcrowded living situations, and access to treatment can all contribute to the prevalence of the disease. A previous example of a syndemic was the AIDS crisis in inner cities in the 1980s and 1990s (Tsai et al., 2015). Recently, the idea of a syndemic has been applied towards the SARS-CoV-2 pandemic. Facets to this syndemic include the socioeconomic inequality between nations and current nation's policies towards vaccine use and distribution. In September of 2020, 13% of the world's population (mainly residing in wealthy nations) had secured 51% of the promised doses (Jecker et al., 2021b). As of May in 2021, only 1% of total vaccine doses produced went to Africa (Jecker et al., 2021a). Many low- and middle-income countries are still lagging in vaccination rates as mentioned previously. These outcomes are evidence for how political situations and vaccine nationalism can contribute to this pandemic in other nations. Each nation can be thought of a social group, each with their own vested interests that lead to their policy and decision making regarding vaccines. Ethical frames of solidarity and utilitarian ethics will be introduced.

Solidarity ethics is the idea of togetherness and interrelatedness. Evidence for the need to follow solidarity ethics include the idea of mutations within countries that have a large population of unvaccinated individuals (Jecker et al., 2021c). As diseases do not respect borders,

it is possible for a mutation in another country to wreak havoc in a country with a high vaccination rate. Previously, this set of ethics has been used to argue for a global coalition to develop a vaccine and to distribute it. Few countries have the ability to develop, manufacture, and distribute a vaccine on their own (Jecker et al., 2021b). Thus, the fight to combat the SARS-CoV-2 pandemic has involved many countries in the development of vaccines and has demonstrated this idea of solidarity. Citizens in South Africa were one of the first to participate in vaccination trials for AstraZeneca's COVID-19 vaccine (Moodley et al., 2021). However, after completion of vaccination trials, South Africa was only able to secure a minimal number of doses at nearly double the price that the EU paid. The citizens and country of South Africa did not reap any benefits from participating in the trials (Moodley et al., 2021). Other companies, such as Sanofi and GlaxoSmithKline, are currently holding their phase 3 trials in countries with low overall vaccination rates such as Ghana and Kenya (Sanofi, 2021). Yet another example is an Israeli coronavirus vaccine pill that will soon begin clinical trials in South Africa (Jeffay et al., 2021).

However, other sets of ethics such as Utilitarian ethics can also be used to argue for a distribution of vaccines on a broader scale. Utilitarian ethics is focused on the action that produces the greatest number of benefits overall (Andre et al., 1989). It can be applied towards the issue of booster vaccines and how that impacts global distribution of vaccines. Ultimately, utilitarianism is a desire to help the most people in need and to uptake the decisions that save the greatest number of lives with the respect to vaccinations. A person that has already received their initial doses of vaccination will be protected against hospitalization and severe disease by around 75% - 95% depending on the vaccine (Katella, 2021). A person that has not received a vaccine will not have any protection against severe illness from the virus. Thus, the most utilitarian

decision would be to provide doses to people who have not received any doses at all as this would benefit the most amount of people.

While the development of vaccines required solidarity among many countries, the distribution of vaccines, so far, has not. Much to the dismay of the World Health Organization (WHO), many nations such as France, Britain, and the United States have begun plans to provide booster shots for the coronavirus vaccine while many low-income and middle-income countries are lagging in vaccinations rates (Keaten, 2021). This is a current example of how a political situation or public policy can exasperate the effects of the pandemic as these policies restrict access of other countries to doses of the vaccine. However, other nations such as China have made decisions that have resulted in the export of over 1 billion vaccine doses (Song, 2021). Russia has taken steps to aid in the technology transfer of their Sputnik V vaccine. Nations such as Peru have plans to set up manufacturing plants to produce the Sputnik vaccine (Sullivan, 2021). Even the United States has donated nearly 200 million doses in light of their decision to proceed booster shots (Reuters, 2021). While my technical project is important and focuses on the production of hundreds of millions of doses for a coronavirus vaccine, the distribution and allocation of those doses are just as equally important.

Research Question and Methods

The research question that will be explored is: How can countries model their distribution of vaccines to have the most utilitarian outcome? I will be applying a utilitarian ethical framework towards the United States, Russia, and China's public policy on the distribution of the vaccines they produce. As utilitarian ethics is focused on outcomes, I need to evaluate the possible actions and the outcomes resulting from those actions. The actions I am going to

evaluate include the donation of vaccines to other countries, a focus on providing vaccinations domestically, and the donation/transfer of technology required to produce vaccinations. Evidence is needed for these outcomes and actions. Evidence will include the United States', China's, and Russia's public health policies regarding booster shots (which can come from state department announcements or speeches), vaccine donations to other countries and COVAX, and domestic vaccinations. Vaccine donations can be tracked through state department announcements and through UNICEF, which tracks which countries have donated vaccines and who they have donated them too (insert source). Based on these actions, I could determine all the ways that each of these three countries have generated vaccine doses since vaccinations began. This can be broken down into actual donation of doses, doses given within their country, promised doses to other nations, technology transfer necessary to make doses, money donated to groups such as COVAX to produce vaccines, and patent waivers that can all contribute to creating vaccine doses. I can further break these numbers down into who these doses have gone to (low, low-middle, and upper-income countries or citizens who have already been vaccinated). What will be the most utilitarian outcome is what produces the greatest good for the greatest amount of people. In this scenario, I believe the most utilitarian outcome is contributing the greatest number of doses overall and ensuring they are going to unvaccinated instead of vaccinated peoples. This question is important as the results and conclusions drawn can provide insight towards how other upper-income nations should proceed on their public policies towards providing doses to other nations or providing booster shots to their own nation.

Conclusion

In conclusion, a design for a coronavirus vaccine manufacturing facility will be completed. The estimated output of this facility will be about 400 million doses per year for a

recombinant vaccine that can be stored at higher temperatures. The millions of extra doses produced of a vaccine that does not require cold chain storage can help increase the capability to vaccinate millions of people around the world. While the capability to produce millions of vaccine doses can be solved with more production, the distribution and allocation of these doses is a major issue. A utilitarian ethical framework will be applied to the public policies of the United States, Russia, and China on their vaccine distribution. As a result of this application, further decisions can be made on which policies lead to the greatest number of benefits.

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