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Techno-Economic Evaluation of Novel SARS-CoV-2 Vaccine Manufacturing in the Insect Cell Baculovirus Platform

Kanya Citta Hani Alifia[1, 2*], Cleo Kontoravdi[1], Zoltán Kis[3], Dianursanti Ismail[2]

[1]*Department of Chemical Engineering, ACE Extension, Faculty of Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom*
[2]*Department of Chemical Engineering, Faculty of Engineering, Universitas Indonesia, Kampus UI Depok, West Java 16424 Indonesia*
[3]*Department of Chemical and Biological Engineering, Sir Robert Hadfield Building, The University of Sheffield, Mappin Street, Sheffield, S1 3JD, United Kingdom*

Abstract. The need to increase the COVID-19 vaccine manufacturing capacity at low to middle-income countries (LMIC) led to a growing focus on Novavax (NVX-CoV2373), a thermostable protein subunit vaccine manufactured using a baculovirus and insect cell system (BICS) platform. This study aimed to conduct a techno-economic analysis to assess the BICS platform of vaccine manufacturing and compare it to the mRNA and the saRNA platform. The data from the Novavax patent for the COVID-19 vaccine formulation and the manufacturing steps were used to simulate the BICS vaccine production in SuperPro Designer. From the techno-economic analysis, the productivity of all platforms was compared in terms of doses/day per L production scale. The saRNA platform's productivity is about 1,000-fold of the BICS platform and 20-fold of the mRNA platform. BICS is a feasible option for LMIC to produce vaccines because the cost per dose is like the saRNA platform, while the mRNA platform's cost per dose is 7 times higher than the BICS and saRNA platforms. However, further optimization is necessary to improve the productivity of the BICS platform to match saRNA's platform.

Keywords: Baculovirus; COVID-19; Insect cell; Techno-economic analysis; Vaccine

1. Introduction

The advancement of modern technology enabled researchers to predict the properties of the COVID-19 virus and apply this knowledge to rapidly develop vaccines that successfully lessened the impact of the COVID-19 pandemic globally as posited by Berawi et al. (2020a, 2020b). As of 2nd August 2022, 5.3 billion people had received at least one dose of vaccine, which accounts for 67% of the world population. In total, 12.36 billion vaccine doses have been administered worldwide (Ritchie et al., 2021). However, there is a clear gap in vaccination rates among countries. High-income countries can administer 100 doses per 100 people on average whereas low-income countries had not even reached a 20% vaccination rate by August 2022 (Ritchie et al., 2021; Irwin, 2021). The manufacturing capacity of COVID-19 vaccines in 2021 was around 8 billion doses a year; a combined capacity of AstraZeneca, Pfizer, Sinovac, Sinopharm, and Moderna (AstraZeneca, 2021;

*Corresponding author's email: kanya.alifia@gmail.com, Tel.: +6281382699460
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Pfizer, 2021; Shumei, 2021; Steenhuysen & O'Donnell, 2021). Although global herd immunity was achieved due to vaccinations, some low-income countries failed to achieve this (Ritchie et al., 2021). As COVID-19 virus rapidly mutated into different variants throughout the years, this highlights the importance of annual booster shots in the future, which adds to the vaccine demands (O'Neill, 2021). Thus, it is necessary to increase the vaccine manufacturing capacity mainly aimed for low to middle-income countries (LMIC).

RNA vaccines such as Pfizer and Moderna require ultra-cold storage at -70°C and -20°C, respectively (Gerhardt et al., 2021). The distribution of these vaccines is challenging in warmer areas where access to an ultra-cold supply chain is insufficient. Other vaccine types such as inactivated whole virus, viral vector, and protein subunit only require 2-8°C temperature for storage in a refrigerator, with Novavax (2021a, 2021b) as the leading example. Novavax (NVX-CoV2373) is a protein subunit vaccine with 89.3% efficacy against multiple variants in its phase 3 trial conducted in the UK (Novavax, 2021a). It is manufactured using a baculovirus and insect cell system (BICS) platform. A platform technology can be used to manufacture various vaccines simply by modifying the genetic sequence of the cloned baculovirus. Adopting a platform technology will improve the resilience capacity of biopharmaceutical industries to be prepared against future pandemics. Vaccine production using platform technology have more robust and rapid productivity. Moreover, a platform technology is adjustable to produce different vaccines (Sofyan et al., 2021).

BICS is a well-established platform for vaccine manufacturing using recombinant DNA technology, it can produce three different vaccine types: recombinant proteins as subunit vaccines, virus-like particles (VLPs) as subunit vaccines, and recombinant baculovirus as vaccine vectors. The vaccine development process starts with modifying the recombinant baculovirus to contain the gene of interest from the native virus. This gene can either encode the formation of protein subunits, the construction of VLPs, or produce antigens to be carried by the baculovirus vectors (Mena & Kamen, 2011). The insect cells act as the host, which contains the necessary organelles for heterologous protein production and can rapidly construct the desired component (Sari et al., 2016). Insect cells have a higher reproduction rate than mammalian cells and contain a protein folding mechanism that bacteria lack, highlighting the advantage of the BICS platform (Mena & Kamen, 2011).

To make Novavax vaccines, the genetic sequence of SARS-CoV-2 spike protein is cloned into baculovirus culture to infect Sf9 insect cells for the protein folding process. The expressed antigen protein is then purified as multimeric nanoparticles and configured with saponin-based Matrix-M™ adjuvant to enhance neutralizing antibodies and increase long-lasting B-cell and T-cell immunity (Novavax, 2021b). This vaccine is thermostable, adaptable to new COVID-19 variants, feasible for rapid large-scale production, and can be produced with standard equipment (Novavax, 2016 & 2021c). Novavax released its patent for SARS-CoV-2 vaccine formulation in March 2021, showing the manufacturing steps and the trials that were taken to determine the optimum formulation of antigen substance and adjuvant (Novavax, 2021c). This patent was used to build the vaccine production flowsheet with SuperPro Designer software; a process simulator that facilitates the modelling, evaluation, and optimization of integrated biological and chemical processes. Meanwhile the mass balances in the bioreactors are calculated by accounting for the insect cells metabolic fluxes to estimate the stoichiometric reaction equation (Carinhas et al., 2011; Gioria et al., 2006).

It is beneficial to compare Novavax's insect cell vaccine with the mRNA (messenger RNA) vaccine and novel saRNA (self-amplifying RNA) vaccine, to find out which platform can achieve the target vaccine cost per dose of 1 USD (Kis et al., 2020a). A comparative study

of various vaccine platforms had been commenced with the indicators such as technology readiness, complexity, ease of scale-up, flexibility, vaccine thermostability, and speed of response. These indicators show that RNA and BICS platforms are nearly up to par, but a more detailed feasibility study must be done with techno-economic analysis (Kis et al., 2019). Moreover, Kis et al. also conducted a techno-economic simulation of the mRNA and saRNA vaccine platform, which will be the benchmark for BICS platform performance (Kis et al., 2020b). This study aimed to conduct a techno-economic analysis to assess the BICS platform for COVID-19 vaccine manufacturing using SuperPro Designer software and compare it with previous findings.

2. Methods

A literature review was conducted to gather information regarding COVID-19 vaccine production processes in the BICS platform. The step-by-step production process and the costs are taken from Novavax patents (2016, 2021c), scientific literature (Kis et al., 2020a; Kis et al., 2019; Sari et al., 2016; Mena & Kamen, 2011), and trusted suppliers such as ThermoFisher, Sigma Aldrich, Cytiva Life Sciences, and GE Life Sciences. The production flowsheet was designed according to the block flow diagram of CoV-S protein vaccine production in BICS from the Novavax patent, especially for the parameters of the bioreactor and downstream processes (Novavax, 2021c; Kis et al., 2019). Additional data was obtained from the SuperPro Designer equipment, materials, utilities, and cost databases. The demand for BICS vaccines was estimated at 3 billion doses, considering by 2021 that 8 out of 11 billion doses had been met by existing manufacturers.

2.1. Simulation of COVID-19 Vaccine Production in BICS Platform

The vaccine production process was modeled using SuperPro Designer version 12 from Intelligen, Inc starting from the upstream, midstream, until downstream assuming fed-batch operation mode. The formulation and the fill-to-finish line were not simulated in SuperPro Designer since it is usually done in a separate facility. This bioprocess simulation tool can calculate the material and energy balances, equipment sizes, labor requirements, and optimal scheduling of operations and procedures. SuperPro Designer version 12 can also procure an economic evaluation using its built-in database, user-specified costs, and selling prices (Canizales et al., 2020).

For the upstream and midstream processes, the cultivation of Hi-5 insect cells is done using a 5-500 L disposable bioreactor and then scaled up into a 2000 L seed bioreactor, while the virus amplification is done in a separate line with Sf-9 insect cells in 5-500 L disposable bioreactors. In the next step, the baculovirus transfects the insect cells in a 2500 L bioreactor to instruct the cells to express the spike protein antigen of the SARS-CoV-2 virus (Novavax, 2021c; Kis et al., 2019). The duration of cell culture in the main production bioreactor lasts 48-96 hours (Novavax, 2021c). The stoichiometric reaction equation for the Sf9 insect cell growth phase, the Hi5 insect cell growth phase, and the baculovirus infection phase are modelled according to the metabolic fluxes of the cells (Carinhas et al., 2011; Gioria et al., 2006). This equation is necessary to model the mass balances inside the bioreactors.

The downstream separation step starts with centrifugation to separate the cells from the liquid medium, then mixed with Triton X-100 for cell lysis. Then the mixture is passed through the microfiltration step to separate the antigen polypeptides from cell debris. Polypeptide nanoparticles are formed using a detergent exchange method in a sequence of affinity chromatography, where the first column uses NP9 detergent, and the second column uses PS80 detergent. The result will be trimers of polypeptides or glycoproteins

attached to a detergent core. For the downstream purification, the mixture undergoes dialysis of CoV-S polypeptide in a solution of sodium phosphate, NaCl, and PS80, as well as ultrafiltration. The mixture is frozen until it is ready for the formulation step in another facility, to be mixed with excipients and Matrix-M™ adjuvant. The CoV-S polypeptide drug substance per vaccine ranges between 5-45 µg/dose based on the clinical trial (Novavax, 2021c). The block flow diagram of COVID-19 vaccine production in the BICS platform is shown below (Figure 1). This diagram only shows the production of the CoV-S spike protein antigen, which is the active ingredient in COVID-19 vaccines. Further processing, such as formulation and packaging, are typically conducted in a different plant, which are not accounted for in this simulation flowsheet.

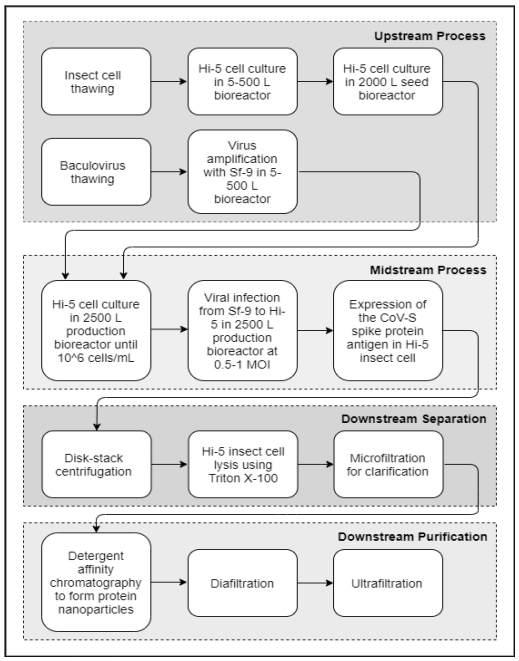


Figure 1 Block flow diagram of COVID-19 vaccine production in baculovirus-incest cell system (BICS)

2.2. Simulation of COVID-19 Vaccine Production in mRNA and saRNA Platform

The simulation for both platforms was done in a previous study by Kis et al. (2020b). In the upstream process, the DNA template is generated, amplified in E. coli culture, purified, and linearized. In the midstream process, the RNA is synthesized with in vitro transcription reaction and 5' cap analogs are used for the 5' capping of the RNA to ensure antigen expression. It is then purified and formulated in lipid nanoparticles or polycationic formulations to maintain its stability. The operation runs as a batch process that lasts 11 hours from start to finish. For self-amplifying RNA (saRNA) vaccines, each dose contains 0.1-10 µg drug substance while for mRNA vaccines each dose contains 25-250 µg drug substance (Kis et al., 2019). The result from this study was compared to the techno-economic analysis results of the BICS platform.

3. Results and Discussion

3.1. Techno-Economic Analysis of BICS, mRNA, and saRNA Platform

A comparison of techno-economic analysis between BICS and mRNA platforms is conducted to assess which platform can fulfill global vaccine demands at the lowest cost possible. The novel saRNA platform is also compared against these two platforms due to its rapid production rate with less than 10 L reactor size (Kis et al., 2019), showing potential

for high-level productivity. The Phase I clinical trial showed 87% effectiveness in 192 people aged 18-45, thus more studies are needed to assess the safety and immunogenicity of saRNA vaccine in other age groups and with a higher number of test subjects (Pollock et al., 2022).

The base case was calculated at the median value of all process input parameters (process scale, process failure rate, production titer, basic labor rate, CoV-S protein amount per dose, and cost of lab/QC/QA) which then resulted in a particular production titer, while the lower and upper case were calculated using ± 20% margin of the production titer differences from the 10.5 g/L base case. The upper-case scenario is when the process produces +20% production titer or 12.6 g/L, while the lower-case scenario is when the process makes -20% production titer or 8.4 g/L (Kis et al., 2020b). The summary of process input parameter values for the BICS simulation is shown in Table 1.

Table 1 Input parameters and their respective ranges, central values, and distribution

Parameter name and unit	Value of input parameter	Reference
Process scale [L]	2,500	(Novavax, 2021c)
Process failure rate [%]	2,500	(Novavax, 2021c)
Production titre [g L^{-1}]	10.5	(Novavax, 2021c)
Basic labor rate [USD $hour^{-1}$]	20	(Petrides, 2021)
CoV-S protein amount per dose [µg $dose^{-1}$]	25	(Novavax, 2021c)
Cost of Lab/QC/QA [% of total labor costs]	40	(Petrides, 2021)

3.1.1 Comparison of CAPEX and OPEX

The capital expenditure (CAPEX) and annual operating expenditure (OPEX) were calculated by SuperPro Designer and then compared between BICS, mRNA, and saRNA platforms (Figure 2).

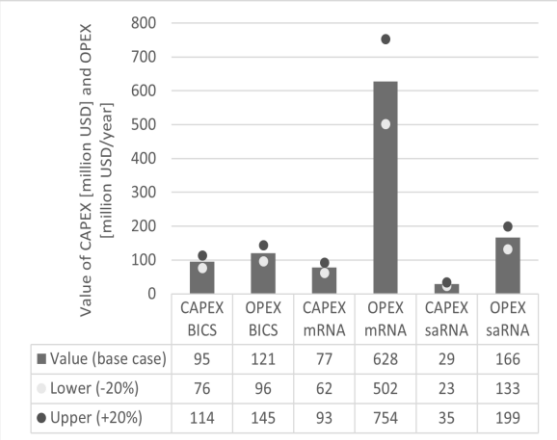


Figure 2 CAPEX and OPEX of vaccine production in BICS, mRNA, and saRNA platform

The BICS platform has the highest value of capital expenditure (CAPEX) at 76-114 million USD, followed by the mRNA platform at 62-93 million USD, then the saRNA platform at 23-35 million USD. The high CAPEX in the BICS platform is due to the significantly higher production scale. The process also involves an upstream process of the Hi-5 insect cell culture line and virus amplification line in the Sf-9 insect cell, which does not exist in RNA-based vaccine production. The main contributors to the CAPEX in the BICS platform are equipment purchase, installation, engineering, and construction fees.

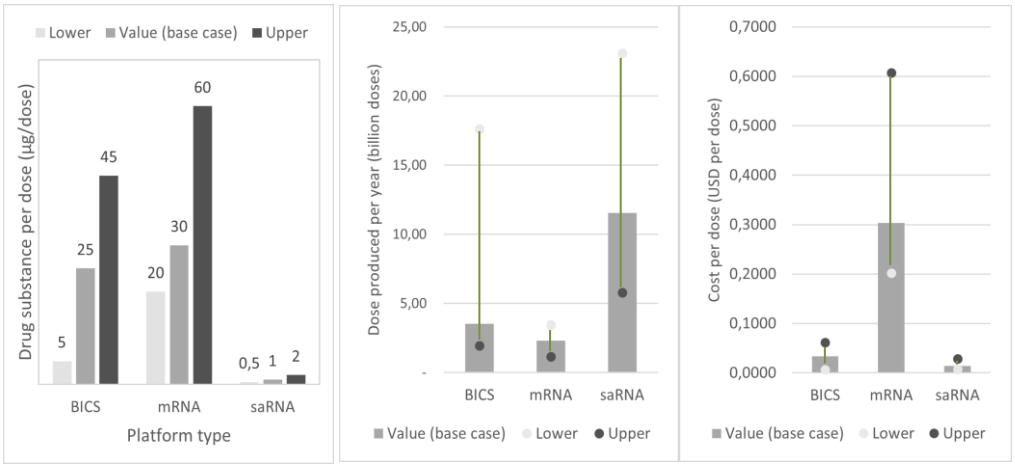
The CAPEX of the mRNA platform is 20% lower than the CAPEX of the BICS platform, while the CAPEX of the saRNA platform is 70% lower than the CAPEX of the BICS platform.

The smaller production scale of RNA platforms reduced the cost of equipment purchase and installation costs, engineering fees, and construction fees. The CAPEX of the mRNA platform mainly consists of the buildings and construction costs because the downstream process for mRNA vaccine drug substance requires multiple steps such as tangential flow filtration (TFF), chromatography, microfiltration, and dialysis, thus still needing enough space in the plant layout (Petrides, 2021). The equipment cost and installation cost are still lower because of the reduced scale compared to the BICS platform. The main contributor of CAPEX in the saRNA platform is the same as the mRNA platform due to the high similarity of the production process in both platforms.

The annual operational expenditure (OPEX) of mRNA platform is at 502-754 million USD. That is about 4 times larger than the OPEX of the saRNA platform at 133-199 million USD and even 5 times larger than the OPEX of the BICS platform at 96-145 million USD. The main reason the OPEX of the mRNA platform is very high is the raw material cost, mainly the CleanCapAU priced at 340,000 USD per kg and the UTP priced at 230,000 USD per kg, which contribute to 35% and 24% of the total raw material costs, respectively. With a price this high, it will be helpful to research any substitute material or find ways to produce these at a lower cost. Using single-use equipment for storage, mixing, and production of drug substances also adds to the consumable costs. Overall, the raw materials and consumables costs are 74% and 24% of the total OPEX, respectively.

3.1.2. Comparison of cost per dose and productivity

The amount of drug substance per dose varied based on the clinical trials of each vaccine type as shown in Figure 3a (Novavax, 2021c; Kis et al., 2020b). The variations of scenarios would affect the number of doses produced per year and correspond to the lower case, base case, and upper case. The cost per dose is calculated by dividing the annual OPEX by the annual doses produced. The yearly doses produced and the cost per dose are presented in Figure 3b and Figure 3c. The production scale of BICS, mRNA, and saRNA platforms are set at 2500 L, 30 L, and 7 L, respectively (Novavax, 2021c; Kis et al., 2020b). The prices for adjuvants (Matrix M and saponin) are considered additional costs that increase the cost per dose (SigmaAldrich, 2021).



(a) (b) (c)

Figure 3 a) Drug substance per dose; (b) Vaccine doses produced per year; (c) Production cost per dose

The productivity of each platform was obtained by dividing the doses produced per year by the working days (assumed to be 330 days), then dividing it again with the production scale volume. This calculation used the base values from the range of inputs and

the practical working days to obtain the productivity value. The saRNA platform's productivity is about 1,000-fold of the BICS platform and 20-fold of the mRNA platform. The saRNA and BICS platforms are economically up to par according to the cost per dose, while the mRNA platform's cost per dose is 7 times higher than the BICS and saRNA platforms. These are shown in Table 2.

Table 2 Productivity of BICS, mRNA, and saRNA vaccine production platform presented as doses per day per L bioreactor

Platform	Doses/year	Doses/day	Production scale (L)	Productivity (Doses/day per L)
BICS	±3,500,000,000	±11,000,000	2,500	±4,000
mRNA	±2,300,000,000	±7,000,000	30	±200,000
saRNA	±11,500,000,000	±35,000,000	7	±5,000,000

The smaller production scale of saRNA compared to the mRNA platform significantly reduced the volume of CleanCapAU needed thus reducing its OPEX. The mRNA platform has a higher throughput per year at 69.04 kg of the drug substance while the saRNA platform only produced 11.55 kg of the drug substance. Comparing the production cost per kilogram product shows the value for the saRNA platform at 14.4 million USD per kg and the mRNA platform at 10.1 million USD per kg. BICS platform remained the most economically feasible option at 1.3 million USD per kg product and 92.66 kg of the drug substance annual throughput.

The OPEX of the BICS platform is mainly dominated by the cost of baculovirus and insect cells (both Hi-5 and Sf-9) as well as the consumables cost such as the disposable bioreactor and Capto Lentil Lectin column (3400 GBP for 5 x 5 mL set) for the chromatography process (SigmaAldrich, 2022; ThermoFisher, 2022; SigmaAldrich, 2021; Cytiva, 2020). With the reproductive nature of insect cell culture, the cell line and scaling up process do not require a lot of new cells and are only necessary to maintain the insect cell culture in an optimum reactor condition and medium content. The large production scale provides a higher annual throughput of 23 kg than the mRNA platform. The base case for drug substance per dose for BICS and mRNA is quite similar, thus their annual dose produced is only 1 billion doses apart. With a significantly lower OPEX per kilogram drug substance than mRNA and saRNA, the BICS platform can manufacture vaccines as rapidly as mRNA with an almost 90% cheaper production cost per dose. Although saRNA has the highest production cost per kilogram product at 14.4 million USD per kg, the ultra-low dosage at 1 µg/dose enables the platform to produce 11.5 billion doses annually. This drives the cost per dose even lower than the BICS platform.

The smaller productivity (doses/day per L production scale) in the BICS platform is due to the vast difference in production scale between the BICS platform and both RNA-based platforms. The substantially lower amount of RNA drug substance per dose for the saRNA vaccine also contributed to more rapid production of vaccine doses compared to mRNA and BICS. When investing in a vaccine manufacturing platform, there will be a trade-off to consider between platform productivity and the cost per dose (Kis et al., 2020b). When saRNA is ready for large-scale manufacturing after multiple phases of clinical trials and assessment of current Good Manufacturing Practices (cGMP), it will be fair to consider this platform for vaccine production. Overall, the BICS platform shows a significant advantage over the mRNA platform both technologically (annual production of vaccine doses) and economically (cost per dose). The lower productivity will be a challenge for further research on optimizing the production scale and productivity.

4. Conclusions

Baculovirus and insect cell system (BICS), mRNA, and saRNA platforms were evaluated for their techno-economic feasibility to manufacture the SARS-CoV-2 vaccine rapidly using SuperPro Designer. From the techno-economic analysis, the saRNA platform's productivity is about 1,000-fold of the BICS platform and 20-fold of the mRNA platform. The saRNA and BICS platforms are economically up to par, as shown by their similar cost per dose, while the mRNA platform's cost per dose is 7 times higher than BICS and saRNA platforms. However, it is best to focus on developing the BICS platform for SARS-CoV-2 vaccine manufacturing in LMICs because it is more clinically developed than saRNA, which by 2021 had not reached the clinical trials step while BICS had passed its third clinical trial. Further research is needed to consider other costs in the techno-economic analysis and optimization study of the BICS platform to improve its productivity and lower its capital cost.

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