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Vaccine production and supply need a paradigm change

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Abstract

We discuss the impact of COVID-19, the journey towards developing vaccines against the disease, and how biomanufacturing should evolve in order to meet similar challenges in the future.

KEYWORDS

biomanufacturing, bioprocessing 4.0, biotechnology, COVID-19, vaccines

SARS-CoV-2 has been circulating in the global population for a little less than 2 years now. In this time, COVID-19 has claimed over 5 million lives and has caused immeasurable economic and psychological damage.[1,2] The global scientific community initiated over 300 vaccine projects in response to the pandemic. At the time of this writing, a total of 22 vaccines have now been approved by health authorities around the world, and another 91 are currently undergoing clinical testing.[3,4] All the approved vaccines comprise either the whole, inactivated SARS-CoV-2 virus; or a viral vector or messenger RNA that encodes the expression of the virus' spike glycoprotein; or simply a sub-unit of the spike protein.[4,5] Sinovac's vaccine is an example of an inactivated, whole virus, whereas the AstraZeneca and Johnson & Johnson (J&J) vaccines are adenovirus-based vaccines. On the other hand, the Pfizer and Moderna vaccines are examples of mRNA vaccines, while the Russian-developed EpiVacCorona vaccine contains a portion of the peptide sequence of the SARS-CoV-2 spike glycoprotein. Surveillance of the approved vaccines suggests that not only do they offer protection against COVID-19 but they have also reduced transmission of the disease.[6] Yet, instead of raising cheerful visions of a post-pandemic age, the global endeavour to develop vaccines against COVID-19 has laid bare some uncomfortable truths about vaccine manufacturing, limitations in the supply chain, and persistent inequities in access to vaccines.[7–11] As many as 12 billion doses will be needed in order to attain herd immunity globally. However, only 7.6 billion doses have been administered thus far, owing to manufacturing and distribution challenges.[12] The entire continent of Africa has hitherto received less than 2% of these doses.[13] About 42% of the global population has been fully vaccinated but most of these reside in the developed world.[12]

The slow roll-out of vaccines is in stark contrast to the alarming speed with which variants of SARS-CoV-2 are emerging around the world. It is estimated that the virus exhibits a nucleotide substitution rate of 1×10^{-3} substitutions per year, which translates to a single nucleotide change for every 1000 nucleotides in its genome each year.[6] Of particular concern are the B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), and B.1.617.2 (delta) variants, which were first identified in the United Kingdom, South Africa, Brazil, and India, respectively.[14] The alpha, beta, and gamma variants bear the N501Y substitution in their spike glycoproteins, whereas the beta and gamma variants also exhibit the E484K substitution and a mutation at the K417 position (N and T for beta and gamma, respectively).[6] The delta variant, on the other hand, bears L452R and T478K substitutions. Similarly, the P681 position is mutated in the alpha and delta variants (H and R for alpha and delta, respectively). These mutations have been shown to increase the binding

affinity of the spike glycoprotein to the ACE2 receptor of epithelial cells that line the nasal cavity, which ultimately makes the variants more infectious and transmissible.[6,15] In addition, the alpha variant also has two amino acid deletions at the 69 and 70 positions. The deletions allow the virus to efficiently evade the immune response of the host, making it particularly life-threatening.[16] All COVID-19 vaccines that are currently in distribution are based on the spike glycoprotein of the original SARS-CoV-2 virus that was first identified in Wuhan, and it is still uncertain if any of these vaccines deliver the same, high levels of protective immunity against emerging variants.[17,18]

The longer it takes to administer the 12 billion doses needed for global herd immunity, the more likely it is that one or more variants will emerge that are sufficiently divergent to completely evade the immunity conferred by current vaccines. In light of current levels of international mobility, resistant variants will eventually spread around the world and potentially unleash greater chaos on civilization. No country will be safe as long as the disease rages in other parts of the world. Even in the rare and fortunate event that a resistant variant does not emerge, existing vaccines will still need to be constantly redesigned and reformulated in order to ensure continued protection against closely related variants.[19] Current and future demand for COVID-19 vaccines—not to mention vaccines for other diseases such as influenza—will severely stretch the global vaccine supply chain, possibly to its breaking point. Effective suppression of COVID-19 and other infectious diseases will require disruptive innovations that make vaccine manufacturing and distribution more responsive, more agile, and more economical to rapidly meet evolving global demand.

The production of the immunogenic agent is the most important step in the vaccine manufacturing and supply chain. Production of adenovirus-based vaccines commences with the propagation of the virus particles in specialized producer cells that are cultured in single-use bioreactors.[20] For instance, the AstraZeneca COVID-19 vaccine is produced in HEK 293 cells, whereas the J&J vaccine is cultivated in PER.C6 cells. The bioreactors are precisely controlled to minimize process variations that could have a detrimental effect on product quality, and the use of single-use fermentation equipment simplifies logistics, shortens batch times, and reduces the risk of contamination.[21] The viral particles are recovered from the producer cells through chemical lysis, which is then followed by normal flow filtration to concentrate and clarify the product. The clarified vaccine is further purified using membrane chromatography and subsequently re-buffered using ultrafiltration to prepare it for formulation into the finished vaccine dose. The manufacture of the Pfizer and Moderna mRNA vaccines, on the other hand, commences with the production of plasmid DNA that comprises the coding sequence for the mRNA transcript.[22] The plasmid is typically produced in *Escherichia coli*, and the construct is subsequently purified and linearized for in vitro transcription in a cell-free reaction mixture. The mRNA product necessitates the addition of a 5′ guanylyl cap and 3′ polyadenylic tail to enhance its stability and prevent immune rejection by the body.[23] These modifications are accomplished enzymatically either during or after transcription.[22] Like the adenovirus vaccines, the mRNA vaccine product is also purified using chromatography and then conditioned using ultrafiltration. The purified vaccine products are then formulated into injectable doses, which then undergo "fill and finish" into vials. All in all, vaccine manufacturing typically requires in excess of 200 components, including the immunogenic agent, glass vials, filters, latex, tubing, adjuvants, stabilizers, emulsifiers, and disposable bags.[5,7,24] Each of these components is manufactured in strict compliance with good manufacturing practices (GMPs) in regulated facilities around the world, and a shortfall in any one item could destabilize the entire supply chain.[25]

The production of the immunogenic agent incurs the highest regulatory overheads of all of the aforementioned steps. As a consequence, it is only practical on a large scale in centralized manufacturing facilities that have been designed to lower costs, eliminate redundancies, and improve efficiency. These facilities typically incur capital expenditures ranging between $50–300 million depending on their size and complexity and additional operating expenditures that are roughly 20% of capital costs.[26] In light of these capital and technological requirements, vaccine manufacturing is concentrated in a few nations, notably India, China, South Korea, the United States of America, the United Kingdom, and Germany. In fact, over 90% of the global requirement for COVID-19 vaccines will be manufactured in these nations.[27] Ergo, the subsequent distribution of vaccine doses from a handful of production sites to all corners of the globe presents a formidable logistical challenge. The World Health Organization (WHO) has attempted to unclog this bottleneck by supporting initiatives to increase vaccine production in developing countries and has also backed a proposal led by India, South Africa, and other members of the Developing Countries Vaccine Manufacturers Network (DCVMN) to temporarily waive intellectual property protections for COVID-19 vaccines.[28–31] The DCVMN comprises as many as 43 vaccine manufacturers spanning 14 countries and currently contributes over half of UNICEF's annual vaccine requirements.[28] Its proponents claim that approval of the DCVMN's proposal could bolster localized production and lead to short-term self-sufficiency in the developing

world for the remaining duration of the pandemic, but the proposal is controversial and is unlikely to be approved in the near term.[28–30,32] In addition, the WHO is coordinating the delivery of formulations from vaccine manufacturers to companies with facilities for filling and packaging injectable drugs in various parts of the world.[33] Still, it is abundantly clear that widespread distribution of effective vaccines—all vaccines, not just those for COVID-19—necessitates the use of innovative formulations and cold chain logistical solutions that increase the shelf life of the product. The requirement for cold storage is particularly acute for the mRNA COVID-19 vaccines, as evidenced by recommended storage temperatures of −70 and −20°C for the Pfizer and Moderna vaccines, respectively.[34] The AstraZeneca vaccine has a more conventional recommended storage temperature of 4–8°C. Cold chains significantly increase the costs of vaccines and the logistical complexities involved in distributing them.[35] The cost of a new vaccine is typically as high as $3–5 per dose.[36] Manufacturing accounts for about half of this cost, and filling, vialing, packaging, and transport account for the other half. The AstraZeneca COVID-19 vaccine falls into this price range.[37] However, the Moderna and Pfizer vaccines cost $37 and $20, respectively, owing to the additional costs involved in formulating and distributing these products at their recommended storage temperatures, as well as a global paucity of key ingredients required for their manufacture.[33]

Tectonic changes are currently afoot in the world of manufacturing. Sensors and computing systems are now deeply embedded within manufacturing processes. These devices are connected to each other and the internet.[38] The vast volumes of data that they continuously upload to the cloud are being analyzed using artificial intelligence to control and optimize processes in real-time. Moreover, advanced robotics has been integrated within manufacturing chains to improve the efficiency of material handover between unit operations. These developments, which are collectively referred to as "Industry 4.0", have improved productivity and product quality and have facilitated autonomous operation and decentralized decision making.[39] Not to be left behind, biopharmaceutical companies too have embraced digitization and automation. However, their use has been generally limited to optimizing expression systems for protein production and improving the integrity and scale of cell banks for biomanufacturing.[40,41] There is a clear opportunity for “Bioprocessing 4.0” to take root in the industry, especially since it is a natural evolution of quality-by-design (QbD), which seeks to integrate data analysis and risk management into process development in order to achieve consistent and high product quality at reduced costs.[42] The global pandemic has brought to light the vital need to accelerate clinical testing and process development and adopt QbD approaches much earlier in the value chain, possibly at the R&D stage. In particular, Bioprocessing 4.0 could transform vaccine production and distribution and lead to the development of intensive, decentralized biomanufacturing platforms, especially in resource-limited settings.

Single-use or disposable bioreactors are now commonplace in the biopharmaceutical industry and have been successfully incorporated into pre-clinical, clinical, and production-scale biotechnological facilities over the past few years.[43] Disposable bioreactors are pre-sterilized by gamma irradiation and can be directly deployed for vaccine production without cleaning and steam sterilization. Moreover, given their simplicity, they are considerably cheaper to operate, relatively easier to control using Internet-of-Things (IoT) devices, and more economical at lower scales compared to conventional bioreactors. In fact, rapid, low-cost fabrication of single-use bioreactors has already been achieved in academic and research settings,[44] including our laboratories. We propose moving one step further towards single-use, integrated systems.

In one manifestation of our vision, decentralized vaccine production can be achieved by utilizing a library of standardized templates and off-the-shelf parts, potentially making any home or facility an impromptu manufacturing site. Standardized components can be printed anywhere with the click of a button for cents. By utilizing polycarbonate (a common 3D printing filament), the system could also be easily sterilized.[45,46] It would be fully modular, with each of the chambers housing a distinct unit operation. The fluid transfer would be achieved with the usage of peristaltic pumps, allowing for an entire closed-loop system. We especially advocate the use of cell-free reaction mixtures for the synthesis of the immunogen since it could further reduce costs and solve the challenges of product traceability and quality that traditionally plague decentralized bioprocesses.[41,47,48] Likewise, the high yields inherent in cell-free reactions allow for smaller working volumes to be utilized. A wide range of products can be produced on-site depending on the DNA template that is inserted. The cell-free reaction mixtures can also be lyophilized and loaded into the system along with desiccated salt mixtures for the required buffers. In this scheme, merely injecting water into the system through an appropriate filter could kick-start the production train. The entire process would be fully automated through the use of a network of Arduino microcontrollers connected to Raspberry Pis. Low-cost (non-contact) sensors and analytical devices such as near-infra-red (NIR) systems can track the process and facilitate real-time optimization. Consistent with QbD principles, machine learning could be employed to relate how media composition and processing

parameters influence yields, productivities, and titers and subsequently distil these insights into a vastly smaller set of easily measurable metabolites that could be tracked using low-cost sensors.[49,50] Likewise, mixing and temperature control in the chambers could also be achieved using low-cost instrumentation. These capabilities will lead to improved process monitoring and control schemes, both of which are essential for improving biomanufacturing outcomes and lowering costs. Most of these components are available at a reasonably low cost, and the system envisioned here would cost ~$500–2000 to manufacture, depending on the complexity of the reactor desired. Moreover, localizing production at the point-of-use also greatly simplifies formulation, potentially eliminates the need for cold-chain supply, and greatly reduces the reliance on cold storage, thereby drastically reducing the cost of a single dose.

The version of the integrated, single-use system described here reduces the need for the establishment and operation of standalone production facilities that incur high capital and operating expenses and are inflexible towards product switching. Many variations of this system are conceivable, and such innovations will ultimately translate to significant savings for healthcare systems, particularly in the developing world. We also advocate for the establishment of open standards and technologies to facilitate greater collaboration and data sharing in order to accelerate innovation-at-scale and overcome market and regulatory uncertainties. Such a model for innovation has already been successfully deployed in advanced manufacturing under the aegis of the Open Manufacturing Platform, which includes companies such as BMW, Microsoft, Anheuser-Busch InBev, and Bosch,[51] and it is high time for the biopharmaceutical industry to follow suit.

AUTHOR CONTRIBUTIONS

Athanasios Kritharis: Conceptualization; writing – original draft; writing – review and editing. **I. Melih Tamer:** Conceptualization; writing – original draft; writing – review and editing. **Vikramaditya G. Yadav:** Conceptualization; writing – original draft; writing – review and editing.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

[1] E. Dong, H. Du, L. Gardner, *Lancet Infect. Dis.* **2020**, *20*, 533.
[2] D. M. Cutler, L. H. Summers, *JAMA-J. Am. Med. Assoc.* **2020**, *324*, 1495.
[3] G. Forni, A. Mantovani, *Cell Death Differ.* **2021**, *28*, 626.
[4] COVID-19 Vaccine Tracker, https://bit.ly/3n7eBd8 (accessed: April 2021).
[5] A. Irwin, *Nature* **2021**, *592*, 176. https://doi.org/10.1038/d41586-021-00727-3.
[6] A. C. Darby, J. A. Hiscox, *BMJ* **2021**, *372*, 771.
[7] J. B. Ulmer, U. Valley, R. Rappuoli, *Nat. Biotechnol.* **2006**, *24*, 1377.
[8] R. Rao, B. Schreiber, B. Y. Lee, *Vaccine* **2017**, *35*, 2103.
[9] COVID Vaccine Supply Is Causing an EU Crisis–So What's Being Done to Speed Up Production?, https://bit.ly/3tWgf3G (accessed: March 2021).
[10] E. Aryeetey, E. Engebretsen, Å. Gornitzka, P. Maassen, S. Stølen, *Lancet* **2021**, *397*, 23.
[11] The Cold Supply Chain Can't Reach Everywhere–That's a Big Problem for Equitable COVID-19 Vaccination, https://bit.ly/3rlq6ht (accessed: March 2021).
[12] Our World in Data: Coronavirus (COVID-19) Vaccinations, https://ourworldindata.org/covid-vaccinations (accessed: April 2021).
[13] Less than 2% of World's COVID-19 Vaccines Administered in Africa, https://bit.ly/3x7wQDQ (accessed: April 2021).
[14] A. Rambaut, E. Holmes, Á. O'Toole, V. Hill, J. McCrone, C. Ruis, L. du Plessis, O. Pybus, *Nat. Microbiol.* **2020**, *5*, 1403.
[15] R. Mason, *Eur. Respir. J.* **2020**, *55*, 2000607.
[16] R. Challen, E. Brooks-Pollock, J. M. Read, L. Dyson, K. Tsaneva-Atanasova, L. Danon, *BMJ* **2021**, *372*, 579.
[17] R. Rubin, *JAMA-J. Am. Med. Assoc.* **2021**, *325*, 1241.
[18] New COVID Variants Have Changed the Game, and Vaccines Will not Be Enough. We Need Global 'Maximum Suppression', https://bit.ly/3dNYNJh (accessed: April 2021).
[19] E. Callaway, H. Ledford, *Nature* **2021**, *590*, 15.
[20] S. V. Vemula, S. K. Mittal, *Expert Opin. Biol. Th.* **2010**, *10*, 1469.
[21] P. F. Stanbury, A. Whitaker, S. J. Hall, *Principles of Fermentation Technology*, 3rd ed., Butterworth-Heinemann, Oxford, UK **2016**.
[22] N. A. C. Jackson, K. E. Kester, D. Casimiro, S. Gurunathan, F. DeRosa, *NPJ Vaccines* **2020**, *5*, 11.
[23] A. Shatkin, *Cell* **1976**, *9*, 645.
[24] P. Gomez, J. Robinson, in *Plotkin's Vaccines*, 7th ed. (Eds: W. Orenstein, P. Offit, K. M. Edwards, S. Plotkin), Elsevier, Amsterdam, The Netherlands **2018**, p. 51.
[25] International Federation of Pharmaceutical Manufacturers and Associations, *Towards Vaccinating The World: Landscape of Current COVID-19 Supply Chain and Manufacturing Capacity, Potential Challenges, Initial Responses, and Possible "Solution Space"*, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland **2021**. https://www.ifpma.org/wp-content/uploads/2021/03/Summit_Landscape_Discussion_Document.pdf (accessed: July 2021).
[26] R. Douglas, V. Samant, in *Plotkin's Vaccines*, 7th ed. (Eds: W. Orenstein, P. Offit, K. M. Edwards, S. Plotkin), Elsevier, Amsterdam, The Netherlands **2018**, p. 41.
[27] Where Coronavirus Vaccines Will Be Produced, https://www.statista.com/chart/23885/coronavirus-vaccine-production-capabilities-by-country/ (accessed: July 2021).

[28] B. Hayman, S. Pagliusi, *Vaccine: X* **2020**, *5*, 100066.
[29] Biden Commits to Waiving Vaccine Patents, Driving Wedge with Pharmaceutical Companies, https://www.washingtonpost.com/health/2021/05/05/biden-waives-vaccine-patents/ (accessed: July 2021).
[30] DG Calls on COVID-19 Vaccine Manufacturers to Increase Production in Developing Countries, https://bit.ly/3bfbdrU (accessed: July 2021).
[31] Waive COVID Vaccine Patents to Put World on War Footing, https://www.who.int/news-room/commentaries/detail/waive-covid-vaccine-patents-to-put-world-on-war-footing (accessed: July 2021)
[32] Merkel Pushes Back on Vaccine Patent Waiver in Row with U.S., https://www.bloomberg.com/news/articles/2021-05-06/merkel-pushes-back-on-vaccine-patent-waiver-in-clash-with-biden (accessed: July 2021).
[33] The COVID vaccine challenges that lie ahead, https://www.nature.com/articles/d41586-020-03334-w (accessed: July 2021).
[34] Covid: What do We Know about China's Coronavirus Vaccines?, https://www.bbc.com/news/world-asia-china-57817591 (accessed: July 2021).
[35] C. Saroja, P. Lakshmi, S. Bhaskaran, *International Journal of Pharmaceutical Investigation* **2011**, *1*, 64.
[36] M. Papania, D. Zehrung, C. Jarrahian, in *Plotkin's Vaccines*, 7th ed. (Eds: W. Orenstein, P. Offit, K. M. Edwards, S. Plotkin), Elsevier, Amsterdam, The Netherlands **2018**, p. 1320.
[37] The Cost per jab of COVID-19 Vaccine Candidates, https://bit.ly/3nZWTJ9 (accessed: July 2021).
[38] What is Industry 4.0?, https://ibm.co/3lVqgNR (accessed: July 2021).
[39] The Fourth Industrial Revolution: What It Means, How to Respond, https://bit.ly/3CrGnIE (accessed: July 2021).
[40] M. Wilson, Why Bioprocessing 4.0 Is a Force to Be Reckoned with, https://www.bio-itworld.com/news/2019/10/15/why-bioprocessing-4-0-is-a-force-to-be-reckoned-with (accessed: July 2021).
[41] M. May, *Genet. Eng. Biotechn.* **2020**, *40*, 42.
[42] The advantages of a 'Quality by Design' approach in pharma drug development, https://www.pharmamanufacturing.com/articles/2019/the-advantages-of-a-quality-by-design-approach-in-clinical-and-commercial-pharma-development/ (accessed: July 2021).
[43] R. Eibl, S. Kaiser, R. Lombriser, D. Eibl, *Appl. Microbiol. Biot.* **2010**, *86*, 41.
[44] T. Lücking, F. Sambale, S. Beutel, T. Scheper, *Eng. Life Sci.* **2015**, *15*, 51.
[45] Sterile 3D Printing Materials for Medical Devices, https://bit.ly/30I8iWl (accessed: November 2021).
[46] G. Shea, K. Wu, I. Li, M.-F. Leung, A. Ko, L. Tse, S. Pang, K. Kwan, T.-M. Wong, F. Leung, C. Fang, *3D Printing in Medicine* **2020**, *6*, 7.
[47] K. Khambhati, G. Bhattacharjee, N. Gohil, D. Braddick, V. Kulkari, V. Singh, *Frontiers in Bioengineering and Biotechnology* **2019**, *7*, 248.
[48] C. Chiba, M. Knirsch, A. Azzoni, A. Moreira, M. Stephano, *BioTechniques* **2021**, *70*, 2.
[49] M. Serra, C. Brito, C. Correia, P. M. Alves, *Trends Biotechnol.* **2012**, *30*, 350.
[50] K. Campbell, J. Xia, J. Nielsen, *Trends Biotechnol.* **2017**, *35*, 1156.
[51] Accelerating Manufacturing Innovation at Scale: Solving Mutual Challenges through Open Collaboration, https://bit.ly/3ixnlc2 (accessed: July 2021).

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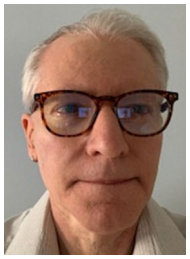

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