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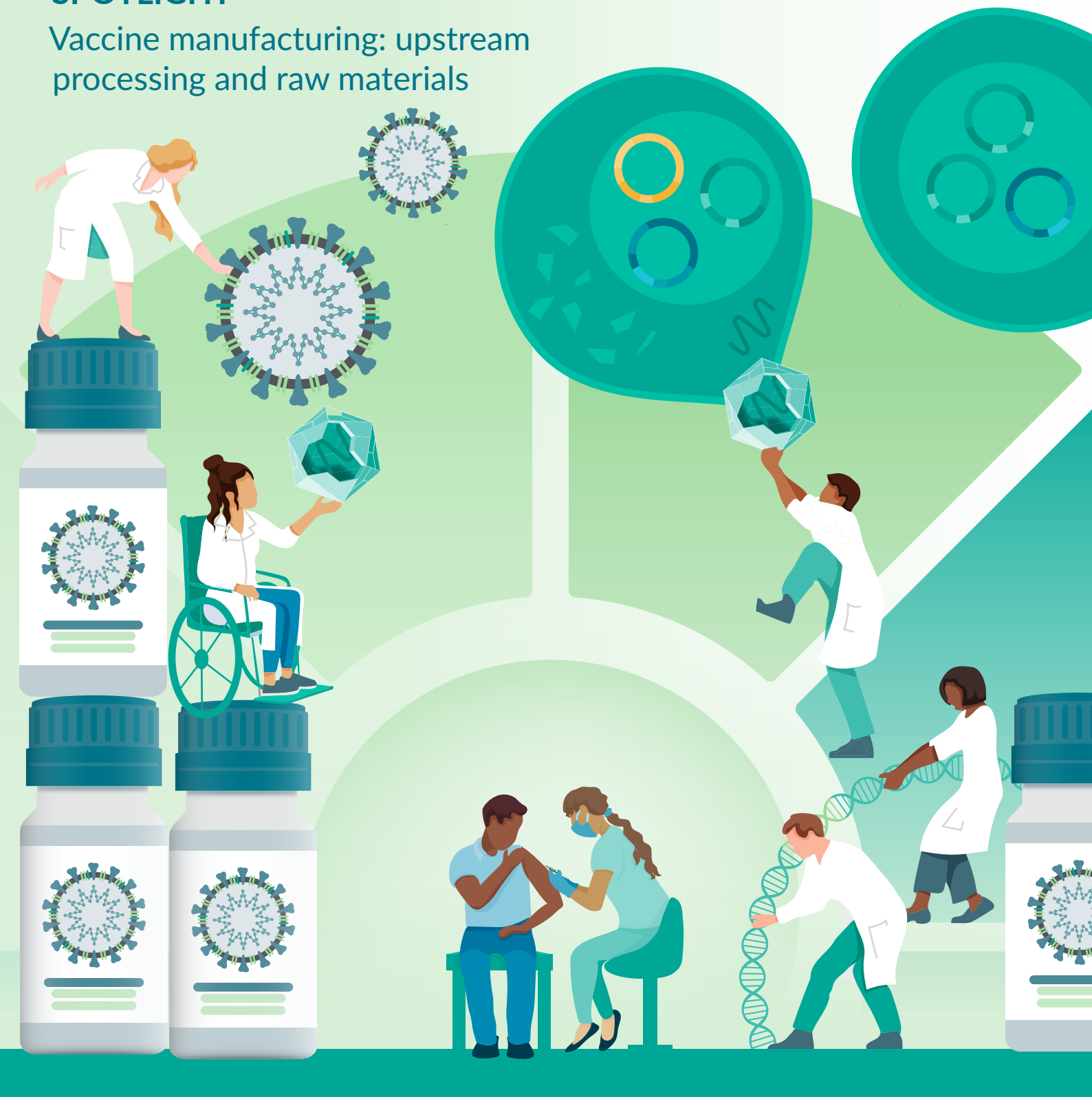
VACCINE INSIGHTS

SPOTLIGHT

Vaccine manufacturing: upstream processing and raw materials



VACCINE INSIGHTS

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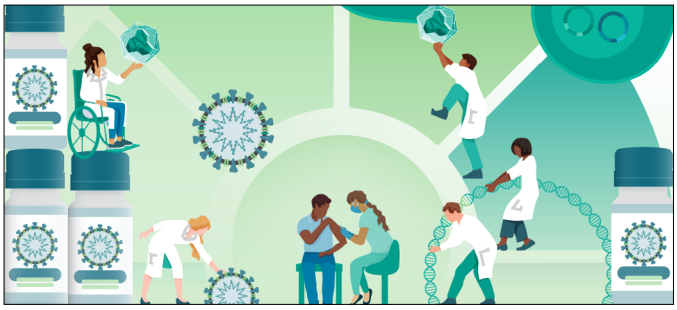

VACCINE MANUFACTURING: UPSTREAM PROCESSING AND RAW MATERIALS

SPOTLIGHT

EXPERT INSIGHT

RISING STARS

Towards deterministic bioprocesses

This article is part of our 'Rising Stars' series, giving a platform to the emerging leaders of the sector. In this series, we share the perspectives of fledgling thought-leaders, chosen by our Editorial Advisory Board members as future stars in their field.

Sam Reffsin was nominated by Editorial Advisory Board member Christopher Ton, Principal Scientist, Vaccines & Advanced Biotechnologies Process Development, Merck & Co.

While robustness in a bioprocess is defined by the consistent achievement of product quality despite internal and external variabilities, the reality of biological plasticity often leads to heterogeneous cellular phenotypes within isogenic populations. This insight article explores the implications of biological nondeterminism for bioprocess development, emphasizing the importance of systems biology approaches and advanced molecular engineering to optimize robustness and yield. Techniques such as single-cell genomics, DNA barcoding, and *in silico* modeling, which provide insights into cellular heterogeneity and enable the mapping of cell states across dynamic bioprocess phases, are discussed. Additionally, the need for proactive engagement with regulatory agencies, particularly in the context of bridging clinical trials when modifications to the way approved products are manufactured occurs, is highlighted. By reevaluating legacy processes and implementing a pre-investment strategy in systems biology, the field can enhance product manufacturability and ensure compliance with evolving regulatory standards. The goal of deterministic bioprocessing in vaccine production addresses the inherent biological nondeterminism observed in cellular systems, ultimately supporting the development of safe and effective vaccines.

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BIOLOGICAL NONDETERMINISM

Robustness refers to a system's ability to maintain its functions despite external and internal disturbances. In bioprocess development, robustness is a crucial attribute, as it ensures that the same product quality is achieved with defined inputs. However, defining and controlling bioprocess robustness is challenging, as the term 'robustness' itself can be complex. Biological systems are notably robust,

yet they are also nondeterministic [1–6]. In computer science, nondeterminism denotes the uncertainty of an outcome due to multiple possible results, even when the same inputs are applied [7,8]. In essence, biology is inherently plastic. This plasticity contributes to biological robustness, enabling biological systems to evolve and adapt efficiently to both micro and macroenvironmental changes, thereby gaining a selective advantage.

What does biological nondeterminism mean in the context of vaccine manufacturing? For a specific input, such as a stable cell line expressing an antigen, it implies that individual cells within an isogenic population can exhibit divergent phenotypes [9–16]. These cells share the same genotype, yet their phenotypes can differ for various reasons. Subtle variations in a cell's microenvironment may activate specific signaling pathways in one cell but not in another. In Crabtree positive *Saccharomyces cerevisiae* microbial fermentation [17], for example, one cell may find itself in a local minimum of glucose availability, prompting it to utilize alternative sugar sources. In contrast, another cell might be in a local maximum of glucose availability, allowing it to ferment the glucose efficiently. The variability in nutrient mixing and the challenges associated with controlling these factors present an intriguing scale-dependent challenge, although this topic will not be addressed further here [18–20].

There are also molecular drivers of heterogeneity in cell phenotype. A cell's past can influence its future; that is, its experiences can be encoded as epigenetic memory [21–25]. This memory can manifest through various modifications to a cells ability to express certain genes or loci (without a change in genotype), such as methylation or histone modifications. Epigenetic memory can take on multiple forms. During development, cells undergo differentiation and experience epigenetic changes that establish gene expression patterns defining their cell type [21,22]. In both therapeutic protein and vaccine bioprocessing, cells of a specific type—or even those derived from a single clone—are often utilized, which may render developmental memory less relevant compared to other fields, such as cell therapy [26,27]. Additionally, cells can acquire environmental memory. Stressors such as nutrient limitation, toxins, or other stressors can induce widespread epigenetic changes that may be inherited by future generations, priming them to respond more effectively to repeated exposure to the same stress. This phenomenon of transgenerational epigenetic inheritance is a critical consideration in the context of bioprocessing. In addition to stress related selective pressure that can drive genetic mutations, a cell's past experiences can lead to stable epigenetic changes being passed on to its descendants [16,23,24,28]. This underscores the importance of developing a comprehensive understanding of the entire bioprocess and associated stressors, from cell banking to harvest.

Practically speaking, what does biological nondeterminism mean for bioprocessing? There are two key considerations: robustness and optimization. In the context of robustness, this concept suggests that to effectively control robustness at the level of individual cells within a process, advanced control strategies that extend beyond traditional process engineering may be necessary, such as molecular engineering. If not all cells are behaving identically in a bioprocess, there may be an opportunity to understand the circuits that drive some cells to perform as intended, as well as the circuits that lead others to engage in undesirable behaviors. The critical questions then become: how can we encourage all cells to act as one within bioprocess? Can we identify biological levers, in addition to process levers, to control the system in a more deterministic manner?

THE APPLICATION OF THE SYSTEMS BIOLOGY TOOLBOX TO BIOTHERAPEUTICS AND VACCINE BIOPROCESS DEVELOPMENT

The field of single-cell biology has evolved from a philosophical digression to a major focus area in quantitative biology and biomedical research. In the last decade, there has been an explosion of new technologies that enable us to apply modern molecular biology techniques to single cells. Additionally, recent years have seen a revolution in big data analytics, predictive modeling, and the ability to construct biological models *in silico*.

MEASURING CELL TO CELL VARIABILITY IN BIOPROCESS

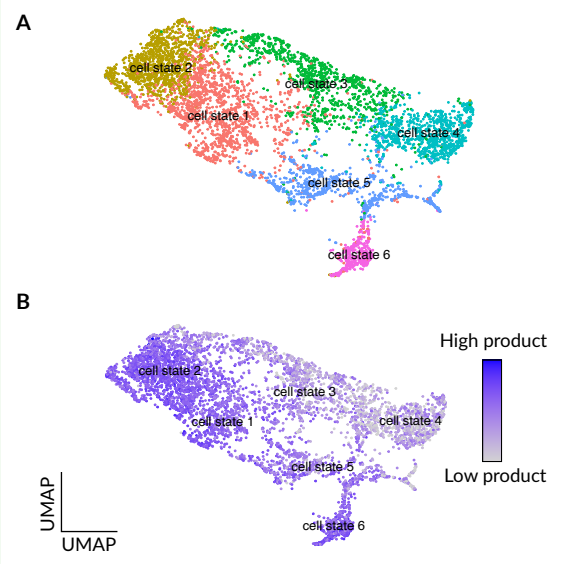
Regardless of whether one is aiming to produce a live virus, peptide, or protein vaccine, most bioprocess development begins with the selection of a cell line as a host. From this point, a single clone is typically chosen based on a set of desirable attributes such as growth rate, productivity, and metabolite profile. This single clone is then expanded and banked for future use. While all cells derived from a single clone are presumed to share the same genotype, they do not necessarily exhibit the same phenotype [16]. In the context of bioprocess, this phenotypic variability may result in differences in production expression across individual cells and perhaps even drift in process behavior over multiple batches and time. Single-cell genomics, particularly transcriptomics, provides a powerful tool for mapping heterogeneity in cell states that are inferred to relate to specific phenotypes and process attributes [29–32]. The ability to profile single cells within a process not only allows for the identification of heterogeneity within a system but also facilitates the connection of that heterogeneity to critical process attributes, such as product expression. By linking cell states (marked and color-coded by the numbers 1–6 in Figure 1A) to productivity (Figure 1B), there is potential to steer cells into favorable gene expression programs, ultimately enhancing yield and robustness.

MAPPING CELLULAR STATE TO FATE

There are many variants of single-cell genomics techniques that can be utilized to optimize bioprocesses. Given that a bioprocess is dynamic and often involves multiple stages and manipulations such as changes in nutrient availability, pH, temperature, gas transfer, and redox potential, the ability to connect a cell's state across different phases of the process is crucial for revealing potential sensitivities [18–20]. Several research groups have developed DNA

FIGURE 1

Variability in product expression across single cells as detected by singe cell RNA sequencing.



(A) Single cell RNA sequencing was used to identify heterogeneity in gene expression states within a bioprocess. The data reflects a single time point. Each dot reflects a cell that has been grouped according to its transcriptome. Cells that are colored the same are assigned to the same cell state. **(B)** Normalized product expression. Overlaid transcript expression of the bioprocess product. Each cell is colored by its expression level, with darker blue referring to higher expression. The cell state annotations from **(A)** are carried through.

barcoding strategies to link a cell's state at a specific point in time to its propensity to follow a particular fate trajectory [33,34].

These methods typically involve the introduction of a random sequence of nucleic acids, usually DNA, into the genome of the cell. As the barcode is integrated, it is heritable through multiple cell divisions, enabling the tracking of cell lineages across generations. Alternatively, CRISPR technology can be employed to 'nick' or cut DNA at predetermined silent loci, resulting in the accumulation of mutations that serve as molecular fingerprints for individual lineages [35,36]. In both cases, the barcode information can be recovered simultaneously with single-cell genomics measurements, facilitating the connection between lineage and cell state.

In bioprocessing, establishing a link between a cell's state early in the process and its future productivity is essential for ensuring end-to-end process robustness. Such DNA barcoding strategies are particularly applicable to live virus vaccine bioprocesses. Viruses manipulate their hosts to such an extent that they can become nearly unrecognizable. Thus, connecting a cell's fate (e.g., whether it is infected and how much virus is being produced) to its endogenous state prior to infection poses significant challenges if one relies solely on profiling cells *post facto*. Lineage tracing can help identify cell states that subsequently yield high amounts of viral particles [28]. With this information, it may be possible to enrich for those specific states to improve yields, potentially through manipulating signaling pathways via small molecule additions or through genetic engineering.

IN SILICO BIOPROCESS DEVELOPMENT

The cornerstone of systems biology is the generation of vast amounts of data. While many tools are available to interpret this data in the context of understanding biological circuits that are critical for bioprocess design [37–41], the goal is to enhance the efficiency of, and in some cases replace, resource-intensive experiments.

For instance, predicting how a single clone of a cell line will perform over the long term within a process can be challenging. Initial clone screening is typically conducted in a high-throughput model that does not accurately represent final manufacturing scales [42–44]. The focus during this stage is usually on titer rather than scalability.

Using single-cell genomics, it becomes possible to create molecular fingerprints that not only represent high-yield phenotypes but also identify characteristics of a robust process. By leveraging historical process data from large-scale operations, it is possible to screen novel clones to ensure that they fit holistically into an existing biomanufacturing platform based solely on *in silico* models development with transcriptomic data. This approach not only mitigates risks associated with clone selection but also saves valuable development time and resources—with the potential to screen thousands of clones in the time it may otherwise take to screen dozens.

BUILDING A ROBUST BIOPROCESS HOST

In the previous discussion, various methods to identify the molecular drivers of process yield and robustness were explored. What can be done with this information? In one scenario, cell state can be manipulated through process controls. For example, if a specific metabolic state is found to be directly linked to increased yield, advanced substrate feeding strategies, media supplementation with small molecule signaling modulators, and gas transfer control can be employed to push cells into defined metabolic states.

Recent advancements in targeted functional genomics represent another pathway to building a robust host. It is now possible to tune biological circuits by activating

or repressing transcriptional regulators, knocking out entire coding regions of genes of interest, and introducing targeted point mutations to modify an organism's genetic code [45–51]. These tools serve as standalone screening techniques for rationally designing bioprocess cell lines, in addition to validating other systems biology data.

TRANSLATION INSIGHT

Pre-investment is a necessity to ensure process robustness

The systems biology toolbox is most effective when applied early in the development pipeline, in particular before a process has been defined in full. This approach allows ample time to identify cell states that can be manipulated and to determine the most effective methods for doing so, whether through process controls or molecular engineering. However, this strategy carries associated risks, as it involves pre-investing in potentially costly systems biology efforts to optimize bioprocess performance before a molecule's efficacy in the clinical can be properly evaluated. Nonetheless, pre-investment in systems level approaches to bioprocess development can yield long-term benefits—not only by ensuring the sustained manufacturability of new products in the future but also by fostering cross-modality knowledge that can influence a wide range of programs.

The willingness to re-evaluate legacy products

Technology evolves rapidly. The molecular tools described in this work have largely been commercialized and scaled within the past decade, to the point where they are considered democratized and easily accessible to most institutions [52,53]. However, the timeline for bioprocess development and the lifespan of commercial products often extends well beyond 10 years [53]. Therefore, it is prudent to continuously re-evaluate legacy manufacturing processes. If opportunities for improvement exist—whether from a cost-of-goods perspective or a robustness perspective—there must be a willingness to revisit and reassess even established commercial processes.

Interfacing with regulatory agencies

There are ethical and regulatory considerations with the use of systems level techniques to inform bioprocess development. Constructing *de novo* cell lines requires the use of genetic tools to manipulate cellular architecture, which can introduce complexities in regulatory submissions. As the industry moves towards more sophisticated bioprocessing techniques, including the use of synthetic biology and advanced gene-editing tools, it is crucial to maintain a dialogue with regulatory agencies early in the development process, ensuring compliance with regulatory frameworks while maintaining product integrity.

Furthermore, when changes are made to an approved product, whether in the manufacturing process or the cell line used, in order to ensure a stable and safe supply of product, conducting bridge trials becomes essential. These trials serve to establish the equivalence of the modified process to the original process that was previously validated during clinical trials. Engaging with regulatory agencies early in planning these bridge trials can ensure that the study designs meet expectations and that the data generated will support ongoing compliance with regulatory requirements, ultimately facilitating a smoother pathway for product continuity.

CONCLUDING REMARKS

Applying systems level techniques to bioprocess development underscores the intricate relationship between cellular heterogeneity and robustness in large molecule

pharmaceutical manufacturing. This understanding can not only enhance the optimization of bioprocesses but also facilitate the identification of molecular drivers that can be manipulated to improve yield and product quality. Furthermore, the proactive engagement with regulatory agencies is essential to navigate the complexities introduced by the use of cutting-edge biotechnologies. As the field continues to evolve, a commitment to reevaluating legacy processes will be vital in ensuring the continued manufacturability and compliance of safe and effective vaccines. Ultimately, the integration of these methodologies can transform the landscape of bioprocess development, paving the way for more deterministic outcomes in inherently nondeterministic biological systems.

REFERENCES

1. Symmons O, Raj A. What's luck got to do with it: single cells, multiple fates, and biological nondeterminism. *Mol. Cell* 2016; 62, 788–802.
2. Webb AB, Angelo N, Huettner JE, Herzog ED. Intrinsic, nondeterministic circadian rhythm generation in identified mammalian neurons. *Proc. Natl Acad. Sci. USA* 2009; 106, 16493–16498.
3. Hastings HM. Stochastic Information Processing in Biological Systems II—Statistics, Dynamics, and Phase Iransitions. In: *Information Processing in Biological Systems* (Editors: Niiranen S, Ribeiro A). 1985; Springer US, 131–144.
4. Heldt FS, Kupke SY, Dorl S, Reichl U, Frensing T. Single-cell analysis and stochastic modelling unveil large cell-to-cell variability in influenza A virus infection. *Nat. Commun.* 2015; 6, 8938.
5. Snijder B, Pelkmans L. Origins of regulated cell-to-cell variability. *Nat. Rev. Mol. Cell Biol.* 2011; 12, 119–125.
6. Joober R, Karama S. Randomness and nondeterminism: from genes to free will with implications for psychiatry. *J. Psychiatry Neurosci.* 2021; 46, E500–E505.
7. Jones C. Probabilistic Non-Determinism. PhD Thesis, University of Edinburgh, 1990.
8. Cohen J. Non-deterministic algorithms. *ACM Comput. Surv.* 1979; 11, 79–94.
9. Mattiazzi Usaj M, Yeung CHL, Friesen H, Boone C, Andrews BJ. Single-cell image analysis to explore cell-to-cell heterogeneity in isogenic populations. *Cell Syst.* 2021; 12, 608–621.
10. Cotari JW, Voisinne G, Dar OE, Karabacak V, Altan-Bonnet G. Cell-to-cell variability analysis dissects the plasticity of signaling of common γ chain cytokines in T cells. Sci. Signal. 2013; 6, ra17.
11. Sanchez A, Garcia HG, Jones D, Phillips R, Kondev J. Effect of promoter architecture on the cell-to-cell variability in gene expression. *PLoS Comput. Biol.* 2011; 7, e1001100.
12. Ansel J, Bottin H, Rodriguez-Beltan C, *et al.* Cell-to-cell stochastic variation in gene expression is a complex genetic trait. *PLoS Genet.* 2008; 4, e1000049.
13. Wang T, Dunlop MJ. Controlling and exploiting cell-to-cell variation in metabolic engineering. *Curr. Opin. Biotechnol.* 2019; 57, 10–16.
14. Fritzsch C, Baumgartner S, Kuban M, *et al.* Estrogen-dependent control and cell-to-cell variability of transcriptional bursting. *Mol. Syst. Biol.* 2018; 14, e7678.
15. Snijder B, Sacher R, Ramo P, *et al.* Population context determines cell-to-cell variability in endocytosis and virus infection. *Nature* 2009; 461, 520–523.
16. Goyal Y, Busch GT, Pillai M, *et al.* Diverse clonal fates emerge upon drug treatment of homogeneous cancer cells. *Nature* 2023; 620, 651–659.
17. Pfeiffer T, Morley A. An evolutionary perspective on the Crabtree effect. *Front. Mol. Biosci.* 2014; 1, 17.
18. Enfors SO, Jahic M, Rozkov A, *et al.* Physiological responses to mixing in large scale bioreactors. *J. Biotechnol.* 2001; 85, 175–185.

19. Doran PM. Design of mixing systems for plant cell suspensions in stirred reactors. *Biotechnol. Prog.* 1999; 15, 319–335.

20. Anane E, Knudsen IM, Wilson GC. Scale-down cultivation in mammalian cell bioreactors—the effect of bioreactor mixing time on the response of CHO cells to dissolved oxygen gradients. *Biochem. Eng. J*. 2021; 166, 107870.

21. Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev.* 2002; 16, 6–21.

22. Kim K, Doi A, Wen B, *et al.* Epigenetic memory in induced pluripotent stem cells. *Nature* 2010; 467, 285–290.

23. Shaffer SM, Emert BL, Reyes Hueros RA, *et al.* Memory sequencing reveals heritable single-cell gene expression programs associated with distinct cellular behaviors. *Cell* 2020; 182, 947–959.e17.

24. Shaffer SM, Dunagin MC, Torborg SR, *et al.* Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance. *Nature* 2017; 546, 431–435.

25. Reyes Hueros RA, Gier RA, Shaffer SM. Non-genetic differences underlie variability in proliferation among esophageal epithelial clones. *PLoS Comput. Biol*. 2024; 20, e1012360.

26. Simaria AS, Hassan S, Varadaraju H, *et al.* Allogeneic cell therapy bioprocess economics and optimization: single-use cell expansion technologies. *Biotechnol. Bioeng*. 2014; 111, 69–83.

27. Kirouac DC, Zandstra PW. The systematic production of cells for cell therapies. *Cell Stem Cell* 2008; 3, 369–381.

28. Reffsin S, Miller J, Ayyanathan K, *et al.* Single cell susceptibility to SARS-CoV-2 infection is driven by variable cell states. *bioRxivorg* 2023; published online Jul 7. https://doi.org/10.1101/2023.07.06.547955.

29. Tanay A, Regev A. Scaling single-cell genomics from phenomenology to mechanism. *Nature* 2017; 541, 331–338.

30. Kalisky T, Quake SR. Single-cell genomics. *Nat. Methods* 2011; 8, 311–314.

31. Trapnell C. Defining cell types and states with single-cell genomics. *Genome Res.* 2015; 25, 1491–1498.

32. Papalexi E, Satija R. Single-cell RNA sequencing to explore immune cell heterogeneity. *Nat. Rev. Immunol.* 2018; 18, 35–45.

33. Weinreb C, Rodriguez-Fraticelli A, Camargo FD, Klein AM. Lineage tracing on transcriptional landscapes links state to fate during differentiation. *Science* 2020; 367, eaaw3381.

34. Emert BL, Cote CJ, Torre EA, *et al.* Variability within rare cell states enables multiple paths toward drug resistance. *Nat. Biotechnol.* 2021; 39, 865–876.

35. Alemany A, Florescu M, Baron CS, Peterson-Maduro J, van Oudenaarden A. Whole-organism clone tracing using single-cell sequencing. *Nature* 2018; 556, 108–112.

36. Choi J, Chen W, Minkina A, *et al.* A time-resolved, multi-symbol molecular recorder via sequential genome editing. *Nature* 2022; 608, 98–107.

37. Xiao Y, Liu J, Zheng Y, *et al.* CellAgent: an LLM-driven multi-agent framework for automated single-cell data analysis. *bioRxiv* 2024; published online May 17. https://doi.org/10.1101/2024.05.13.593861.

38. Schaefer M, Peneder P, Malzl D, *et al.* Multimodal learning of transcriptomes and text enables interactive single-cell RNA-seq data exploration with natural-language chats. *bioRxiv* 2024; published online Oct 18. https://doi.org/10.1101/2024.10.15.618501.

39. Satija R, Farrell JA, Gennert D, Schier AF, Regev A. Spatial reconstruction of single-cell gene expression data. *Nat. Biotechnol.* 2015; 33, 495–502.

40. Stuart T, Satija R. Integrative single-cell analysis. *Nat. Rev. Genet.* 2019; 20, 257–272.

41. La Manno G, Soldatov R, Zeisel A,*et al.* RNA velocity of single cells. *Nature* 2018; 560, 494–498.

42. Sun T, Zhang Y, Liang H,*et al.* Establishment of a semi-continuous scale-down clone screening model for intensified perfusion culture. *Biotechnol. Lett.* 2024; 46, 1085–1093.

43. Hemmerich J, Adelantado N, Barrigon JM, *et al.* Comprehensive clone screening and evaluation of fed-batch strategies in a microbioreactor and lab scale stirred tank bioreactor system: application on *Pichia pastoris* producing *Rhizopus oryzae* lipase. *Microb. Cell Fact.* 2014; 13, 36.

44. Janakiraman V, Kwiatkowski C, Kshirsagar R, Ryll T, Huang YM. Application of high-throughput mini-bioreactor system for systematic scale-down modeling, process characterization, and control strategy development. *Biotechnol. Prog.* 2015; 31, 1623–1632.

45. Doudna JA, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* 2014; 346, 1258096.

46. Gao Y, Xiong X, Wong S, *et al.* Complex transcriptional modulation with orthogonal and inducible dCas9 regulators. *Nat. Methods* 2016; 13, 1043–1049.

47. Jinek M, Chylinski K, Fonfara I, *et al.* A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 2012; 337, 816–821.

48. Mali P, Yang L, Esvelt KM, *et al.* RNA-guided human genome engineering via Cas9. *Science* 2013; 339, 823–826.

49. Cong L, Ran FA, Cox D, *et al.* Multiplex genome engineering using CRISPR/Cas systems. *Science* 2013; 339, 819–823.

50. Jiang W, Bikard D, Cox D, Zhang F, Marraffini LA. RNA-guided editing of bacterial genomes using CRISPR-Cas systems. *Nat. Biotechnol.* 2013; 31, 233–239.

51. Rees HA, Liu DR. Base editing: precision chemistry on the genome and transcriptome of living cells. *Nat. Rev. Genet.* 2018; 19, 770–788.

52. Kitano H. Computational systems biology. *Nature* 2002; 420, 206–210.

53. Van de Sande B, Lee JS, Mutasa-Gottgens E, *et al.* Applications of single-cell RNA sequencing in drug discovery and development. *Nat. Rev. Drug Discov.* 2023; 22, 496–520.

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VACCINE INSIGHTS

SPOTLIGHT

Resilient and flexible biopharmaceutical supply networks: strengthening the vaccine supply chain through a manufacturing supply chain data exchange

John Dyck and Kelvin H Lee

VIEWPOINT

"...the vast majority of manufacturers of all types still rely on emails, faxes, and phone calls to exchange critical data from their suppliers, often resulting in delays and inefficiencies."

The COVID-19 pandemic exposed important flaws in the inbound supply chain for vaccines. NIIMBL and CESMII are working with key stakeholders to develop a means for vaccine manufacturers and suppliers to share information securely for improved supply chain tracking, resilience, and optimization.

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If anyone still doubted the central importance of the inbound supply chain for vaccine manufacture (and most other areas of our domestic and commercial life), the past few years should have dispelled them. The pandemic, geopolitical unrest, and military action across the world have fundamentally disrupted our globally interconnected supply chains, cutting off cities and global supply hubs, while pressurizing raw material supplies. These global events have exposed and continue to put pressure on the traditional inbound supply chain model, which is rooted in 'just in time' lean manufacturing practices.

It is a shocking and little-known fact that the vast majority of manufacturers of all types still rely on emails, faxes, and phone calls to exchange critical data from their suppliers, often resulting in delays and inefficiencies. This makes anticipating and reacting to day-to-day disruptions a non-trivial challenge, but in the face of COVID-19, proved to be an untenable shortcoming. The barriers to digitizing and automating this end-to-end view of suppliers' manufacturing operations are significant, but so are the benefits. Biopharmaceutical companies understand that while minimal idle capacity and just-in-time inventory models offer certain business benefits, they also present high risk of delays and stockouts when disruptions occur. In the 'new normal', supply chain resilience has become a business imperative and competitive edge, requiring more sophisticated approaches to risk management and contingency planning. Disruption, be it small or extreme, is no longer a question of 'if' but 'when'.

Potential delays or failure points in a vaccine supply chain are too numerous to list here, but include categories such as:

- Unavailability of critical raw materials that meet the unique quality specifications required by the customer or manufacturer (e.g., excipients, adjuvants, media and buffer components, enzymes, lipids, chromatography resins, reagents used in required analytical testing or release methods);
- Stockouts or quality failures involving single-use systems or vaccine product components (e.g., filters, plastic bags, single-use bioreactors, glass vials, syringes, cartridges, needles, diluents, etc.);
- Delays due to failure in meeting analytical specifications for incoming raw materials, in-process materials, vaccine substance or intermediates, or final vaccine product;
- Operational disruptions at manufacturing plant or vaccine substance/intermediate/product storage sites (e.g., power failures, natural disasters, pan/epidemics, or political unrest);
- Lack of regional manufacturing capacity due to unexpected demand surges or loss of access to in-house or contract production facilities;
- Failures in transportation, importation, cold-chain shipping, or distribution;
- Absence of alternative or contingency suppliers or validated manufacturing sites within the approved license;
- Regulatory misalignment across countries resulting in fragmented supply chains during initial license applications or post-approval manufacturing changes.

The need for international, digitally connected, cyber-secure, and collaborative real-time decision-support systems isn't novel. A major obstacle is the lack of standardized data definitions and a trusted

collaborative infrastructure that enables manufacturers and suppliers to share information securely. It's also vital to remove the high setup costs for small and medium-sized manufacturers, which requires open, standards-based technology.

Two manufacturing USA institutes, NIIMBL and CESMII, are working with support from the Gates Foundation to convene key stakeholder groups. They also collaborate with CEPI and other innovators that, in concert with standards bodies and policy makers, represent the innovation ecosystem and critical mass needed to address these challenges. These groups approach solutions in a way that scales up both within the USA and globally, and in a manner that is accessible and sustainable for small and mid-sized manufacturers.

Participants in a recent workshop identified and prioritized the following as the most strategic and high-value use cases that an end-to-end manufacturing supply chain data exchange (MSCDE) should address. Ideally, this effort would be undertaken as an open initiative with a strong focus on industry-led standardization. The three primary use cases are centered around supply chain tracking, resilience, and optimization.

1. **Raw materials attribute analysis and product genealogy tracking.** As global supply chains grow in complexity, manufacturers must know precisely where, when, and how each component of their products is made. Standardizing this process would enhance the consistency, speed, and reliability of raw material analysis, and allow traceability throughout the supply chain from suppliers to final distribution. This capability is critical to address quality issues when they arise.

2. **Collaborative demand sensing and supply chain resilience.** Anticipating and forecasting supply chain gaps will give US manufacturers a competitive advantage. Establishing a common framework for real-time analytics can improve global demand forecasting and enable more agile scaling of production and distribution. Additionally, improved risk mitigation, including anticipating supply substitutions, helps ensure continued product quality and availability.

3. **Flow and schedule/planning optimization.** Optimizing business processes improves productivity and enhances supply chain flow from raw materials to final delivery to the patient. This results in a more efficient and reliable manufacturing and distribution process and ultimately improves the livelihood of vaccine end customers.

In contrast to the current technology landscape, workshop participants emphasized that the MSCDE must be developed as a national resource. It should be intentionally designed to support and democratize access and usability across all levels of supply chain participants, from small and mid-sized businesses to large global enterprises. We look forward to receiving feedback from, and continuing to work with, the community on advancing these ideas.

BIOGRAPHIES

John Dyck has been the CEO of CESMII, The Smart Manufacturing Institute since June 2018. He is known globally as a domain expert on digital transformation in manufacturing operations and supply chains. He was recently awarded a number of patents for the application of AI and analytics in manufacturing workflows and business processes. He was recognized

by the Society of Manufacturing Engineers (SME) as one of '30 Leaders Transforming Manufacturing in the USA'. Prior to joining CESMII, John held senior leadership positions in large corporations like GE and Rockwell Automation, and was effective in raising VC funding and building a successful software startup.

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VACCINE INSIGHTS

SPOTLIGHT

EXPERT INSIGHT

Overcoming CMC, manufacturing, and supply chain challenges in vaccine production: a review of efforts in the Global South, with a focus on Africa

Vishal Mukund Sonje and Valerie Chambard

This article investigates the challenges and potential solutions associated with establishing robust and resilient vaccine manufacturing and supply chains in low- and middle-income countries (LMICs). While these regions face significant constraints in manufacturing capabilities and supply chain logistics, they also present unique potential for scaling up global vaccine manufacturing capacity and, therefore, achieving global health security, equitable access and rapid response in outbreak situations. The article explores the technical, infrastructural, and financial barriers that hinder vaccine manufacturing in LMICs, including limited technical know-how, lack of skilled workforce, and insufficient funding. It also examines supply chain pain points for input materials and distribution of finished goods in these regions. The review highlights successful case studies and innovative approaches being employed, particularly by the Coalition for Epidemic Preparedness Innovations (CEPI) and partners, to overcome these challenges. By addressing the critical need for capacity building and international collaboration, the article aims to provide a comprehensive understanding of the current landscape and prospects of vaccine manufacturing in the Global South.

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Delayed access to COVID-19 vaccines contributed to the disproportionate impact of the disease on certain low- and middle-income countries (LMICs) during the pandemic, particularly affecting African countries. The COVID-19 pandemic has underscored the unequal distribution of vaccine development and manufacturing companies worldwide. Most manufacturers are situated in North America, Europe, India, and China. While there are biologics manufacturers in Latin America, their

capacity is limited and does not cover all areas [1,2]. For the African region, during the pandemic, countries predominantly relied on COVAX and other countries for its supply of vaccines and various medical countermeasures [3].

The existing financial mechanism to address the vaccine demand for public immunization is primarily supported through Gavi, WHO, and UNICEF, specifically, in Latin America (five countries), Southeast Asia (22 countries), African continent (39 countries). Over the next 5 years many countries are expected to transition out of Gavi support, for example, from Africa around seven countries (representing 31% of African population) will move to self-financing. The shift in procurement of vaccines to self-financing or other mechanisms offers opportunities as well as some challenges in creating a globally distributed manufacturing base [4,5].

To enable equitable access in future, one of the prevalent approaches considered is to create globally distributed vaccine manufacturing capacity, supported by vaccine manufacturing platforms that can easily adapt in pandemic situations. During periods when there are no large-scale outbreaks, these platforms can be kept warm and sustainable by manufacturing vaccines in routine immunization [6]. To support resilient local manufacturing capabilities, the African Union and the Africa Center for Disease Control and Prevention (Africa CDC) has set an ambitious target to produce 60% of local vaccine demand by 2040 with an expected total demand estimated at 1.2 billion doses per year. Currently, less than 1% of vaccines required in Africa are manufactured locally [7].

African Vaccine Manufacturing Accelerator (AVMA) [8], developed in partnership with the African Union, aims to accelerate the expansion of commercially viable vaccine manufacturing in Africa. AVMA is an initiative designed to support the growth of vaccine manufacturing in Africa by providing financial incentive to eligible manufacturers, as summarized below:

- US$0.50 per dose for vaccines where the drug substance (DS) is processed in Africa on an AVMA priority technology platform or for AVMA priority vaccines
- US$0.40 per dose: For other qualifying vaccines where the DS is manufactured in Africa
- US$ 0.30 per dose: For vaccines where only fill and finish occurs in Africa, capped at US$1 per vial

The priority vaccines are oral cholera vaccine, malaria, measles-rubella, hexavalent (whole-cell pertussis [DTwP] containing), yellow fever, Ebola with improved thermostability as from -20 °C, rotavirus single-dose blow-fill-seal presentation, pneumococcal (viral vector or mRNA technology platforms as rapid response platforms). The AVMA will play a catalyzing role in the transition to localized manufacturing and provide a pathway to financial sustainability for eligible manufacturers [7].

Secondly, innovative financing mechanisms now put in place will help to accommodate surges in vaccine demand due to outbreaks. Tech transfer for the eight antigens listed above has already been arranged including traditional technologies like live attenuated virus, crucial for high-demand vaccines, and in addition, support is being provided to establish novel platform such as mRNA for new vaccine development, expected to scale as science and investment progress [9].

CHALLENGES IN SETTING UP MANUFACTURING IN THE GLOBAL SOUTH

The limited manufacturing capacity has been identified as a key driver of inequitable access to vaccines in the Global South.

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Other interconnected challenges are emphasized below.

Access to manufacturing technology and platforms

In addition to manufacturing capacity, it is essential that the vaccine manufacturers have access to manufacturing technology. Technology transfers are resource- and time-intensive and often not feasible to achieve results in a short time, especially during pandemic situations. It is a complex issue influenced by economic, political, and commercial factors. Representatives and health policy makers from Global South countries have voiced their concern and highlighted the importance of access to the right technologies [10–12].

Gaps in supply chain of incoming materials

To enable success in creating vaccine manufacturing capabilities among new manufacturers in the Global South, it is critical to develop the supply chain ecosystem. The latter plays a pivotal role, as manufacturers need hundreds of different critical input materials and consumables. Most of these materials are supplied by manufacturers in high-income nations. A lack of pooled and consistent demand, wide geographical spread of recent greenfield vaccine manufacturing sites, lead time disruptions and currency fluctuations make it challenging for input materials manufacturers to localize manufacturing or establish a defined distribution network in the Global South [13].

CEPI'S RESPONSE TO EXPAND VACCINE MANUFACTURING CAPABILITIES AND ASSOCIATED SUPPLY CHAIN IN THE GLOBAL SOUTH

One of CEPI's landmark initiatives is the '100 Days Mission', which aims to develop vaccines against emerging infectious diseases within 100 days of identifying a new threat [14]. This ambitious goal relies heavily on the manufacturing networks established in the Global South, as rapid production and distribution close to the source of an outbreak are critical to the success of the mission. By leveraging the enhanced capabilities of vaccine manufacturers in LMICs, CEPI aims to ensure a swift and effective response to future pandemics, minimizing their impact on global health and economies.

To ensure a rapid response to pandemics, maintaining 'warm' manufacturing capacity is crucial. Developing routine immunization vaccines on novel platforms can help achieve this. While fill-finish capacity is generally product agnostic and adaptable for various vaccines and biotherapeutics, for DS, more effort is needed to bridge the gap between current vaccine platforms and rapid response platforms like mRNA. For other novel platforms, namely viral vector and protein subunit, efforts are ongoing to shift some of the routine vaccines to novel technologies, such as developing measles and rubella vaccine using fixed bed reactors. While most routine immunization platforms differ from novel ones, balancing between traditional versus conventional technologies is necessary.

CEPI has been working on various fronts to facilitate establishing a vaccine manufacturing network in the Global South. Key levers and technical resources [15] of this strategy are:

- Expand vaccine manufacturing network capacity and capability building in LMIC countries
- Streamline the supply chain management and ecosystem
- Strengthen the local regulatory agencies and enabling national control laboratories

- Chemistry manufacturing and control (CMC) templates and guidance
- Tech transfer guidance
- CMC framework—Phase appropriate CMC milestones/guidance [16]
- Best practices for process validation and comparability [17]

In this review, initiatives coming under purview of manufacturing and supply chain are reviewed in detail.

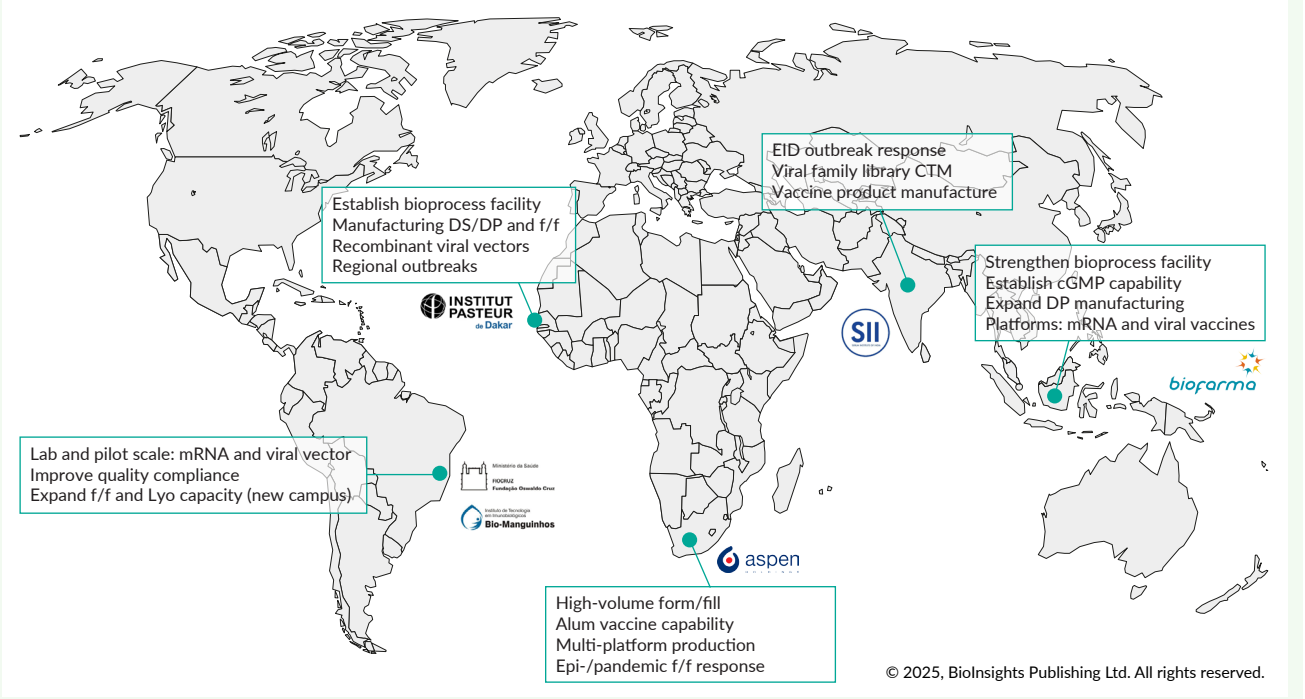
Manufacturing network

CEPI is supporting the establishment of a sustainable vaccine manufacturing network in the Global South. A Call for Proposals was launched in Q1/2022; following a defined eligibility criteria and due diligence process, several vaccine manufacturing organizations from the Global South were selected. Case studies from a few of these partnerships are discussed further below. Details of the current CEPI vaccine manufacturing network are shown in Figure 1.

By fostering partnerships and facilitating technology transfers, CEPI has enabled five manufacturers [18] to access manufacturing platforms capable of rapid response in pandemic situations, such as mRNA or viral vector. CEPI has also supported upgrading the manufacturing capacity, revamping the quality management system and workforce training. Notably, CEPI's support has been instrumental in bolstering existing capacity to ensure that these regions can produce vaccines not only for local consumption but also for global distribution, thereby contributing to worldwide health security.

FIGURE 1

CEPI vaccine manufacturing facility network (VMFN) map.



Five agreements in three different regions supporting manufacturing capacity strengthening in the Global South have been signed.

Broadly, CEPI is supporting VMFN partners to:

- Establish novel platforms capable of rapid response such as mRNA and viral vector
- Upgrade manufacturing capacity to meet current Good Manufacturing Practice (cGMP) standards
- Revamp quality management system and train the local talent on novel platforms

Supply chain management

In 2024, CEPI signed a memorandum of understanding with Africa CDC to strengthen the supply chain and associated vaccine manufacturing ecosystem in the African continent. In the area of supply chain, CEPI collaborates with Africa CDC via the Platform for Harmonized African Health Products (PHAHM), as recently highlighted in [19]. Among several activities, the Framework for Action from PHAHM aims to expand the local manufacturing capacity for Africa to become self-reliant in addressing its vaccination needs in an efficient way, as depicted in detail Figure 2 [20]. Therein, the supply chain related activities fall under the Infrastructure Development program.

With support from local government authorities, donors such as Africa CDC, Gates foundation, CEPI, WHO, Team Europe and IFC, as of today, tech transfer for eight different antigens is in progress in South Africa and Senegal [9]. The current map of sites having signed technology transfer agreement is shown below in Figure 3, with oral cholera vaccine and measles and rubella being DS projects, while yellow fever was an existing vaccine that is currently being upgraded at a new site, with increased manufacturing capacity. The year of product entry to the market indicates the timeline for obtaining WHO prequalification. In addition, there are around 25 vaccine manufacturing initiatives supported by private sector, local government authorities etc. The current tech transfer is mostly focused on building fill-finish

FIGURE 2

Framework For Action for building the African ecosystem required to scale vaccine manufacturing as defined by African Union and Africa CDC [20].

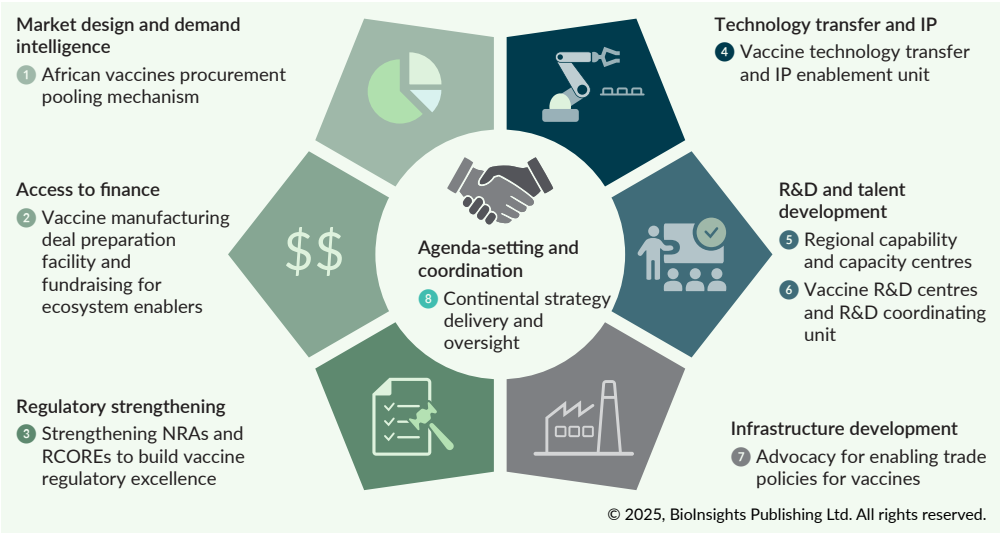
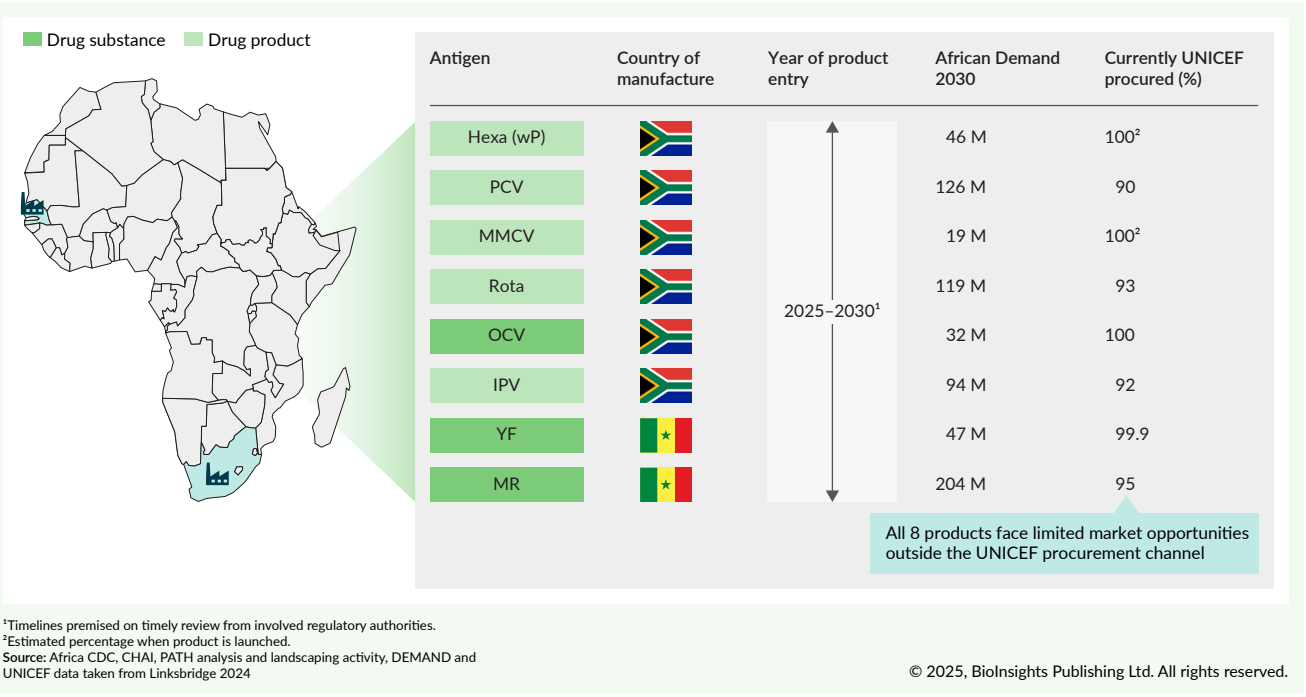


FIGURE 3

African vaccine manufacturing map [9,21].



Eight antigens are expected to achieve WHO PQ and enter the continental market between 2025 and 2030.

capabilities for drug product manufacturing, which is also evident from Figure 3.

The case studies from the ongoing CEPI sponsored projects and tech transfer initiatives are captured below.

Novel manufacturing platforms: mRNA, viral vector and recombinant protein subunit

CEPI is supporting the establishment of novel manufacturing platforms at the VMFN partner organizations. Building on lessons learnt from COVID-19 pandemic, manufacturing technologies and the chosen platforms to implement can readily be adapted for rapid respond in pandemic situations; these technologies are based on mRNA, viral vector or recombinant protein technology. Examples of these are listed below:

- **mRNA technology.** The WHO/MPP mRNA Technology Transfer Program is supported by the WHO and Medicines Patent Pool (MPP). The program's goal is to help LMICs build mRNA development and manufacturing capabilities; and to provide support for access to IP-free raw materials and reagents [21,22]. CEPI-funded mRNA projects are complementary with the WHO/MPP program to support capacity building and utilization. Efforts are also underway to establish comparability with some other prominent technologies, such as Quantoom's mRNA production platforms. mRNA platforms supported by WHO-MPP benefit from pooling the resources for tech transfer, process and analytical development, supply chain management and license-free access to critical components and raw materials [22]

- **Viral vector and protein subunit platforms.** Many LMIC vaccine manufacturers, a few with CEPI support,

are establishing bioprocess labs capable of novel vaccine candidate development, or to receive platform technology. As part of the 100 Days Mission, and particularly the preparedness phase of it, organizations are aiming to have proof of concept immunogenicity studies with exemplar vaccines, and through that, organizations will have standard operating procedures, analytical capabilities and qualified host cell line master cell banks, e.g., MRC5, Vero, CHO, etc. Regional developers/ manufacturers will benefit from having established, well characterized host cell lines and process platforms that can be quickly adapted for novel pathogens. Having integrated bioprocess, scale up and clinical manufacturing combined with platform knowledge in terms of critical process parameters and critical quality attributes will support quickly adapting to include new candidate development [3,18]

GMP or capability upgrade: implementing restricted access barrier systems and filling alum-based vaccines

Existing manufacturing facilities and legacy building in many LMIC regions need upgrading to meet the cGMP standards. For example, the recent revision in EMA Annex 1 mandates the upgrade of cleanroom areas operating under open cleanroom environment to restricted access barrier systems or isolators [23]. These upgrades are crucial for maintaining the highest levels of sterility and ensuring compliance with updated regulatory standards. Implementing such measures significantly reduces contamination risks, enhances product safety, and aligns with the stringent requirements of cGMP. CEPI has supported around four VMFN partners to upgrade legacy filling lines to a cGMP standard [18].

In another instance, the project scope was defined to implement a recirculation loop on the filling line to enable the aseptic filling operation of alum-based vaccines. Adding this capability ensures increased capacity utilization, maintains operational readiness, and prepares the system to respond efficiently in an outbreak situation [18].

Supporting: operations, quality management system upgrade, workforce training

Developing supply chain department in new industry requires input from multiple areas of expertise since such a function has interface with almost all other departments, including planning, finances, procurement, operations, quality, warehousing, and human resources. CEPI supports the development of supply chain strategy by providing technical support, and funding when necessary. CEPI assists one of the VMFN partners by providing consultant support to manage the procurement of laboratory equipment and consumables. Additionally, CEPI provides support to validate supply chain operation modules in enterprise resource planning, through internal expertise.

Another area is upgrading quality management systems from manual to electronic. Secondly, upgrade in the documentation management and/or moving to enterprise resource planning tools, for more efficiency as well as compliance to cGMP requirements.

Supply chain: Africa supply chain forum

Most input materials worldwide come from suppliers in high-income countries. A few global companies dominate the market, creating mutual dependencies (e.g., vials and stoppers). This presents a high-risk situation for supply and business continuity, especially during pandemics or outbreak situations when national protectionist measures, such as export bans, may arise. Input materials currently manufactured in Africa are limited to porcine

gelatin (Gelita/South Africa). In terms of primary packaging materials, Revital™ syringes (Kenya) are prequalified by the WHO. Beyond vaccines, there are tech transfer happening in the biopharmaceutical area [24]. Also, such diversification would support the case for localizing input materials manufacturing in Africa. There are also opportunities for lessons learnt from the tech transfer of other biopharmaceuticals that can be leveraged for vaccines.

In January 2024, CEPI and the Africa CDC co-organized the inaugural supply chain forum in Nairobi, Kenya, dedicated to the African vaccine manufacturing industry [19]. The supply chain forum offered an opportunity for vaccine manufacturers, key suppliers, country representatives, regional representatives, key stakeholders, and donors to discuss their challenges and suggest solutions to address supply chain gaps; some of which are mentioned below.

- Uncertain demand forecasts create supplier backlogs—and manufacturers in the local region are not a top priority for vendors
- Local manufacturers have limited negotiation power due to low and unpredictable demand volumes
- High freight costs arise from long-distance import processing, especially for excipients requiring cold chain
- Import and customs policies lack transparency and vary by country
- Resubmitting import and customs documentation for each transit country adds storage costs and delays
- There is a shortage of skilled workforce in the supply chain, particularly professional buyers who can negotiate favorable payment terms

The above list highlights some of the key issues, and it has a negative effect on production lead time and efficiency. Based on the identified issues, the SC forum recognized three solutions strategies summarized below, and these will be driven through an execution plan also called as roadmap for action:

- **Localize production of key materials.** The scope includes identifying key input materials, geographies and existing support infrastructure. Based on the assessment, to come up with a plan for localizing key materials
- **Regional access and supply consortium.** Developing a pooled procurement mechanism and distribution center to reduce costs through higher volume procurement. This solution requires significant investment and coordination among manufacturers to better standardize inputs. It may be a mid- to long-term solution
- **Simplifying and harmonizing trade regulations, policies and procedures.** Simplification and harmonization of national trade, tariff and import regulations. It also includes roll-out of harmonized system (HS) codes, which are unique identifiers of any material for custom duties and tariffs

To share a practical example of lateral support for supply chain and facilitation during the COVID-19 pandemic, CEPI provided direct support to its partners using a supplier's network developed with the COVAX Marketplace [25]. The principle of the COVAX marketplace was to matchmake between COVID-19 vaccine developers and manufacturers, and suppliers of input materials needed. During the operational period, 14 out of 30 requests raised in the marketplace resulted in a match. Leveraging this experience, CEPI continues

to offer a similar service to connect with suppliers, to speed up access to input materials and consumables needed to develop new vaccines.

Supply chain: mapping the constraints in the incoming materials

CEPI recently sponsored a market research study to map the input materials required for vaccine manufacturing in Africa. It was conducted by a Research Lab Consulting Company, The MindCo. The study aimed to identify pain points in Africa's input-material supply chain and list critical materials to prioritize, along with potential solutions to address these challenges.

MindCo investigated the challenges of procuring input materials and consumables in Africa, primarily by interviewing vaccine manufacturers and input material suppliers. One of the deliverables of the exercise was to identify critical input materials, followed by harmonization and standardization. The assessment resulted in 45 input materials required for drug product manufacturing and quality control, and classified into right categories, as shown in Figure 4. These materials were also categorized based on the level of difficulty of replacing the supplier as per the compliance requirements. The assessment also shed more light on the existing pain points in the input materials supply chain in Africa. Broadly, these pain points fall in two categories—long lead time and high price.

Based on the learning from this analysis and suggestions provided by the stakeholders, the roadmap shown in Figure 5 is currently being built for tackling pain points across the value chain to strengthen the supply chain in Africa.

Developing a sustainable procurement mechanism for African vaccine manufacturers is considered as an enabler for long-term sustainable approaches, such as localization.

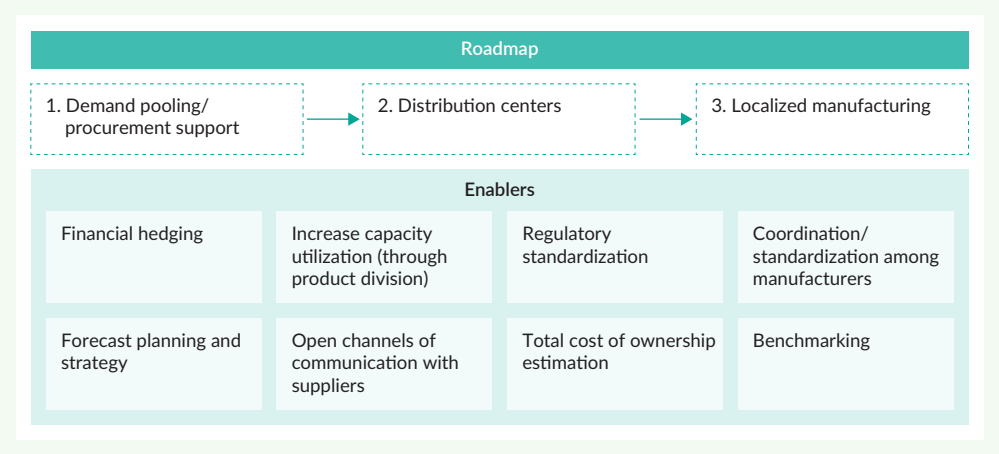
FIGURE 4

List of 45 critical input materials identified based on assessment done by MindCo.

Segment	Category	Number	Input materials
Fill and finish	Adjuvants	6	1. Aluminium-based adjuvants 2. CpG 3. QS-21 4. Squalene 5. Monophosphoryl lipid A (MPL) 6. Liposomal
	Filtration	2	1. Disposable filters 2. Sterile filtration systems
	Lab material	11	1. Connectors 2. Tubes 3. HPLC-columns 4. (q)PCR plates 5. ELISA plates 6. Filters 7. Pipette tips 8. ELISA-assay substrates 9. Pipettes 10. Bags for process and storage 11. (RNase-free), cell culture plates
	Temperature monitoring device	1	1. Vaccine vial monitor (for heat exposure)
	Lab reagents	10	1. (q)PCR-kits 2. Reagents for bioburden 3. Relevant reagents for endotoxin (LAL) 4. Relevant reagents for sterility determination 5. RNA-binding fluorescent dye 6. Relevant antibodies 7. Relevant primers 8. Buffer for the lab 9. Buffer for the pH 10. Cell culture media
	PPE and disposable material	8	1. Connectors 2. Tubes/hoses 3. Filters 4. Pipette tips 5. Pipettes 6. Disposable kits 7. Bags for process and storage 8. Optical adhesive foil
	Primary packaging	4	1. Glass vials 3. Seals/caps 2. Stoppers 4. Ampoules
	Disinfectants	3	1. Decon-quat® 3. Isopropanol 2. Decon clean®

FIGURE 5

Roadmap to build input raw materials supply chain in Africa.



Within the African context, efforts are already underway to harmonize trade procedures across the continent through initiatives from African Continental Free Trade Area and World Trade Organization /World Custom Organization, for example harmonizing the HS codes.

The implementation of a consolidated input material procurement mechanism necessitates several prerequisites, including:

- Demand volume to generate suppliers' interest and long-term engagement
- List of input materials and consumables that do not require long regulatory approval (e.g., tubes, Erlenmeyer flasks, roller bottles and tissue culture flasks, disposable filters, etc.)
- Engagement from all parties such as manufacturers, suppliers, funders, and national government authorities
- Feasibility study with cost estimate and model to cover the inherent costs/overheads

CONCLUDING REMARKS

Building a self-reliant vaccine manufacturing ecosystem in the Global South needs various stakeholders' involvement, including financial support and technical advice, as well as coordinated effort to develop a sustainable manufacturing and supply chain ecosystem. Achieving this goal is a long-term effort, but progress is underway and could be categorized as an early phase in the execution of this program.

To ensure the sustainability of the newly added manufacturing capacity, it is key to expand the scope to diversify the product portfolio beyond vaccines; for example, producing insulin. With an increase in overall turnover and capacity utilization, it will make a good case for materials suppliers and manufacturers to set up a local manufacturing base. Simplification and harmonization of trade regulations and import policies will be critical to this effort.

By focusing on tech transfer, capability building, and developing robust supply chain. CEPI aims to support globally geo-diverse manufacturing capability that can accommodate rapid pandemic response.

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REFERENCES

1. PATH. *Manufacturing Capacity in Latin America: Diagnostics and Vaccines.* https://www.path.org/l/diagnostic-and-vaccine-manufacturing-capacity-in-latin-america (accessed Mar 31, 2025).
2. Pan American Health Organization. *Sustainable Health Agendas for the Americas 2018–2030, Goal 5.* https://www.paho.org/en/shaa2030-goal-5.
3. Khan MI, Ikram A, Hamza HB. Vaccine manufacturing capacity in low- and middle-income countries. *Bull. World Health Organ*. 2024; 99(7), 479–479a.
4. GAVI. *GAVI Impact in Africa Since 2000.* Apr 2024. https://www.gavi.org/sites/default/files/publications/Gavi-in-Africa_FS_2024.pdf (accessed Mar 31, 2025).
5. Gavi Alliance Eligibility and Transition—Policy. https://www.gavi.org/types-support/sustainability/eligibility.
6. Khan MI, Ikram A, Hamza HB. Vaccine manufacturing capacity in low- and middle-income countries. *Bull. World Health Organ.* 2021; 99(7), 479–479a.
7. A breakthrough for the African vaccine manufacturing. *Africa CDC* Dec 8, 2023. https://africacdc.org/news-item/a-breakthrough-for-the-african-vaccine-manufacturing (accessed Mar 31, 2025).
8. AVMA Guidance for Manufacturers. https://www.gavi.org/sites/default/files/support/AVMA-Guidance-for-Manufacturers.pdf.
9. Africa CDC. *African Vaccine Manufacturing Mapping—Supply and Demand Landscape.* Oct 18, 2024. https://africacdc.org/download/african-vaccine-manufacturing-mapping-supply-and-demand-landscape.
10. WHO. *Vaccine Manufacturing Workshop Meeting Report.* Feb 21–22, 2022. https://iris.who.int/bitstream/handle/10665/359113/9789240052017-eng.pdf.
11. Patnaik P. Technology Transfer in Global Health—A Post-Pandemic Reckoning for WHO Member States. *Geneva Health Files* Feb 13, 2025. https://genevahealthfiles.substack.com/p/technology-transfer-in-global-health-who-wto-pandemic-agreement-intellectual-property-trips-voluntary-compulsory.
12. Clinton Health Access Initiative. *Current and Planned Vaccine Manufacturing in Africa*. Sep 21, 2023. https://www.clintonhealthaccess.org/report/current-and-planned-vaccine-manufacturing (accessed Mar 31, 2025).
13. Africa CDC. Africa CDC and CEPI hosts the African Vaccine Manufacturing Supply Chain Forum: future-proofing Africa's vaccine manufacturing supply chains. Feb 1, 2024. https://africacdc.org/news-item/africa-cdc-and-cepi-hosts-the-african-vaccine-manufacturing-supply-chain-forum-future-proofing-africas-vaccine-manufacturing-supply-chains.
14. Collin-Lefebvre T. Progressing the 100 Days Mission for greater global health security. *CEPI* Jan 31, 2025. https://cepi.net/progressing-100-days-mission-greater-global-health-security.
15. CEPI Technical Resources—Manufacturing and Supply Chain Group. https://cepi-tr.tghn.org/manufacturing-and-supply-chain.
16. Särnefält A, Eardley-Patel R, Magini D, *et al.* A strategic guide to improve and de-risk vaccine development: CEPI's CMC framework. *J. Pharm. Sci. Tech*. 2024; 78(5), 613–623.
17. Rovira O. *Platform Protocol Templates*. Oct 19, 2022; CEPI. https://www.casss.org/docs/default-source/cmc-strategy-forum-europe/2022-cmc-europe-speaker-presentations/rovira-olga-cepi-2022.pdf?sfvrsn=c9411453_6.
18. CEPI. Building a global manufacturing network. https://cepi.net/manufacturing-and-supply-chain.
19. Downham M, Bayih AG. Moving forward the vaccine supply chain in Africa. *CEPI* Feb 24, 2025. https://cepi.net/moving-forward-vaccine-supply-chain-africa.
20. Africa CDC. Partnerships for African Vaccine Manufacturing (PAVM) Framework for Action 2022. https://africacdc.org/download/partnerships-for-african-vaccine-manufacturing-pavm-framework-for-action.
21. WHO MPP mRNA program. https://medicinespatentpool.org/what-we-do/mrna-technology-transfer-programme/resources#pills-Technical-Resources.

22. Herder M, Benavides C. 'Our project, your problem?' A case study of the WHO's mRNA technology transfer programme in South Africa. *PLOS Glob. Public Health* 2024; 4(9), e0003173.

23. European Commission. The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing practice for Medicinal Products for Human and Veterinary Use. Feb 21, 2022. https://health.ec.europa.eu/latest-updates/eudralex-volume-4-eu-guidelines-good-manufacturing-practice-medicinal-products-human-and-veterinary-2022-02-21_en (accessed Mar 3, 2025).

24. Aspen announces contract manufacturing agreement to initiate local production of Human Insulin for Novo Nordisk at its Gqeberha based sterile manufacturing facility. *Aspen Pharma* Sep 19, 2023. https://www.aspenpharma.com/aspen-announces-contract-manufacturing-agreement-to-initiate-local-production-of-human-insulin-for-novo-nordisk-at-its-gqeberha-based-sterile-manufacturing-facility.

25. CEPI. CEPI launches COVAX Marketplace to match buyers and sellers of critical manufacturing supplies and speed up global access to COVID-19 vaccines through COVAX. Jul 15, 2021. https://cepi.net/cepi-launches-covax-marketplace-match-buyers-and-sellers-critical-manufacturing-supplies-and-speed.

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VACCINE MANUFACTURING: UPSTREAM PROCESSING AND RAW MATERIALS

SPOTLIGHT

Enabling large-scale production of a next-generation VLP polio vaccine for a post-eradication world

INTERVIEW

"Ideally, we would have a vaccine that could be available under emergency use within the next 4–5 years."

As we move toward a polio-free world, there is a pressing need for alternatives to inactivated and live poliovirus vaccines, which pose an ongoing biosecurity threat. Here, Charlotte Barker, Commissioning Editor, *Vaccine Insights*, talks with Nicola Stonehouse, Professor at the University of Leeds, about a long-running collaboration to develop a virus-like particle (VLP) polio vaccine that can be produced in traditional recombinant expression systems. Plus, an exciting new project is exploring the potential for cell-free production of VLPs.

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Q What are your primary research interests and how have they evolved over time?

NS I'm a virologist. Earlier in my career, I was very much involved in fundamental biology, using viruses as model organisms. It was that fundamental work on the virus lifecycle and the structure of virus capsids that led me to work on vaccines. A pivotal

"...there is a lot of interest in creating virus-free polio vaccines."

moment came in 2011, when I joined a consortium funded by the WHO to explore making a virus-free polio vaccine. That was my first foray into applying basic science to a vaccine problem. At the time, we weren't planning anything beyond proof-of-principle work but has now evolved into a promising candidate virus-like particle (VLP) polio vaccine.

Q What are you working on currently?

NS The lab is still divided between fundamental biology and vaccine work. We are still working on the VLP polio vaccine project, but also applying our successes and lessons learned to other viruses. The fundamental biology involves understanding the complexities of how viral genomes are made and how capsids are assembled. Our research is a mixture of both, and they interplay very nicely.

Q Why is there a need for alternatives to the current polio vaccines as we move toward a post-eradication world?

NS We have two main types of polio vaccine available: an oral vaccine containing a live-attenuated virus, and an injected vaccine containing chemically inactivated virus. Most countries now use the inactivated vaccine. A major disadvantage of both current vaccines is that they require maintaining large stocks of virus, and the consequent biosecurity threat. As we move into a polio-free world, this will become more challenging and expensive. Already many manufacturers are not able to meet the WHO's stringent criteria for manufacturing polio vaccines. By creating a virus-free alternative, we could broaden the number of organizations that can make it.

As well as the threat of biosecurity breaches or bioterrorism, there are long-term polio excretors—people who have had the oral polio vaccine and have not cleared it. Sometimes the virus can be produced in the gut for months, years, and even decades. These people are excreting poliovirus into water supplies, and because the virus mutates readily, this can include viruses that can infect other people. Currently, if we stopped vaccinating, that small number of people could seed a new outbreak. For all these reasons, there is a lot of interest in creating virus-free polio vaccines.

Q What approach is the consortium taking to create virus-free vaccines?

NS Empty capsids are a natural part of the poliovirus lifecycle, alongside capsids filled with viral RNA. The outside surface of these empty capsids is identical to the virus. In theory, if you could produce, harvest, and purify the empty capsids, you would have an effective vaccine. However, empty poliovirus capsids are very unstable and

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rapidly expand into a conformation that is antigenically different. These expanded particles do not generate a protective immune response in verified animal models and so are unsuitable as a vaccine. Our job was to stabilize the VLPs, so they did not expand, keeping the majority in the native conformation.

We initially used structure-based design, but ultimately we found that an evolutionary approach was more effective. We allowed the virus to infect cells under stress, causing the virus to accumulate mutations that stabilized the capsid.

To make a virus-free product, we translated the stabilized particles into a variety of expression systems—plant, insect, mammalian, and yeast. Different partners in the consortium worked on different expression systems—here at Leeds, we are concentrating on yeast.

The first work was done in plants, but we ultimately chose to focus on yeast and insect cell expression systems. The goal behind our work is to translate to as many industrial partners as possible, especially in low- and middle-income countries. It was therefore more strategic to use systems that were already validated and had the potential to produce low-cost vaccines.

Q What are the results so far?

NS The immunogenicity data included in our recent papers [1,2] showed that the VLPs can be as immunogenic as current vaccines when adjuvanted, including when multiple serotypes were mixed. We want to use these VLPs as a combination, not just with each other, but with other components of pentavalent/hexavalent vaccines, to replace inactivated poliovirus in the current childhood vaccination program.

Once we had proof of concept, we started doing yeast fermentation experiments with CPI in Darlington, UK, with additional funding, including from the UK Vax-Hub (led by UCL and University of Oxford). Controlled fermentation improved both the yield and quality of the VLPs produced—and even small improvements in yield can make a big difference when producing billions of doses of vaccine.

In parallel, within the consortium, our colleagues at Oxford are working on scaling up production in insect cells, in the hope of giving manufacturers a choice of expression systems.

Q What have been some of the biggest challenges the consortium has faced in developing the VLP platform?

NS Early on, the biggest challenges lay in generating stabilizing mutations for all three serotypes of poliovirus. NIBSC (now MHRA) played a key role here.

Funding gaps have also been challenging. We have been lucky to be funded via the WHO and the Gates Foundation, but there are often administrative delays at the end of a funding period, and this can create difficulties for research staff working on the project.

"The goal behind our work is to translate to as many industrial partners as possible, especially in low- and middle-income countries."

Our current challenge is purification. We can successfully scale up production in yeast cells but scale-up of purification is still proving challenging.

Q What is the potential for cell-free production methods of VLPs?

NS CPI put together a consortium to look at cell-free production of VLPs, which was recently funded by CEPI. The goal is to be able to make VLPs quickly at the point of care using an automated system, removing the need to stockpile vaccines.

It's early days, but we're aiming to make a variety of VLPs within this system, starting with the core protein from hepatitis B virus and moving on to more complex VLPs like polio.

Q What's next for your work?

NS The VLP vaccine for poliovirus is progressing. We are working with three pharma companies, in India and China, under research agreements, and we are negotiating licensing. We hope to license more widely once the process is fully optimized. Ideally, we would have a vaccine that could be available under emergency use within the next 4–5 years.

Meanwhile, we are continuing with fundamental virology, funded by the NIH. We also have further funding together with UK Vax-Hub to work on viruses related to polio and vaccine platforms for epidemic and pandemic preparedness.

REFERENCES

1. Sherry L, Grehan K, Bahar MW, *et al.* Production of an immunogenic trivalent poliovirus virus-like particle vaccine candidate in yeast using controlled fermentation. *NPJ Vaccines* 2025; 10(1), 64.
2. Sherry L, Bahar MW, Porta C, *et al.* Recombinant expression systems for production of stabilised virus-like particles as next-generation polio vaccines. *Nat. Commun.* 2025; 16(1), 831.

BIOGRAPHY

Nicola Stonehouse is a Professor at the University of Leeds. Her research is both fundamental and applied. Projects involve interdisciplinary teams, and she has expertise leading consortia involving academia and industry. Current projects fall into three main research areas: virus-like particle vaccines for polio and related viruses, fundamental aspects of picornavirus capsid maturation, and picornaviral replication. Nicola studied Biological Sciences (Genetics) at the University of East Anglia, Norwich, UK followed by a PhD in dental enamel development in the Faculty of Medicine, University of Leeds. She moved to the Department of Genetics for post-doctoral studies, applying skills in protein purification and transmission electron microscopy to the study of bacteriophage, working with Peter Stockley. An interest in perusing high-resolution structural studies of RNA-protein complexes led to a long-term collaboration with Lars Liljas' group in Uppsala, Sweden and ultimately led to the award of a Career Development Fellowship from the MRC. Over time, she moved from working on bacteriophage to picornaviruses and was appointed as Lecturer in 2001 and

to Chair in Molecular Virology in 2014. Nicola teaches at all levels and has undertaken a number of roles that aimed to support more junior scientists. She has acted as a member of grant review/interview panels for MRC, Wellcome, Wolfson and BBSRC. She a Fellow of the Royal Society of Biology (FRSB), and the Royal Society for the encouragement of Arts, Manufacture and Commerce (FRSA) and the Higher Education Academy, and was elected to join the Council of the UK Microbiology Society in 2016.

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VACCINE MANUFACTURING: UPSTREAM PROCESSING AND RAW MATERIALS

SPOTLIGHT

Post-pandemic evolution of vaccine development and manufacturing: India and beyond

INTERVIEW

"...we should involve different industries and share the workload so that vaccines can be developed and made available as quickly as possible."

Charlotte Barker, Commissioning Editor, *Vaccine Insights*, speaks with **Sudeep Kumar**, Senior Vice President, Biological E Ltd, about the evolution of the Indian vaccine industry, the growth of vaccine manufacturing in African nations, and the secrets of effective technology transfer and scale up.

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Q How did you first get involved in the vaccine manufacturing field, and how have your interests progressed from there?

SK I have nearly 28 years of experience in biotherapeutics, including significant work in vaccines. My career initially began in the field of recombinant therapeutic proteins and monoclonal antibodies. However, a collaboration with US biotechnology company Novavax during the 2009 H1N1 influenza pandemic marked my entry into the vaccine field. During that period, I visited the USA several times to facilitate technology

transfer for an influenza vaccine, which sparked my interest in vaccine development. Since then, I have overseen the manufacturing of around a dozen different vaccines, including VLP and recombinant vaccines against both viral and bacterial pathogens.

A second significant milestone in my journey was during the COVID-19 pandemic, when I was involved in the rapid development and production of Biological E's successful COVID-19 vaccine.

These two pandemic experiences played a critical role in shaping my interest in vaccine development. Today, I continue to manage several vaccine programs aimed at protecting both adults and children from various infectious diseases. This work is highly motivating, contributing meaningfully to public health by preventing disease and saving lives.

Q Can you tell me about your current role and what it involves?

SK I currently serve as Senior Vice President at Biological E Limited, overseeing the manufacturing of antigens and vaccines. This includes vaccines against a wide range of pathogens, such as hepatitis B, diphtheria, tetanus, pertussis, typhoid conjugate, PCV, and COVID-19.

My responsibilities span various technology platforms, including recombinant protein expression systems, toxoid-based vaccines, and whole-cell bacterial formulations. Each of these requires distinct production approaches, quality standards, and regulatory considerations.

On average, our facilities produce approximately 6 million vaccine doses per day, and I am involved in ensuring consistent quality, regulatory compliance, technology transfer, process optimization, and strategic planning to meet both domestic and global health needs.

Q What are your career highlights to date?

SK There are three key achievements that stand out as the most defining and impactful moments in my vaccine development career. First was establishing the VLP technology platform in India. Our group was the first in the country to set up a VLP technology platform and build a dedicated manufacturing facility to support it.

Second, I was involved in the successful development and launch of the 14-valent pneumococcal conjugate vaccine (PCV14). Overcoming the technical and regulatory challenges associated with such a sophisticated formulation was a major accomplishment.

Lastly, I was deeply involved in the development and launch of a COVID-19 vaccine during the pandemic. Contributing to the rapid development and rollout of an effective vaccine during such a time was both professionally and personally fulfilling.

Q In your view, what lessons did the industry learn from the pandemic?

SK There are two major lessons that I believe the vaccine industry learned from the COVID-19 pandemic. Firstly, that a single company cannot do everything

"India has embraced and advanced several new technologies, including mRNA and DNA vaccine platforms..."

on its own in a pandemic setting. A lot of collaboration and interaction is required between different countries. In such situations, profit margins become secondary to saving lives. Rather than trying to do all activities at a single site, we should involve different industries and share the workload so that vaccines can be developed and made available as quickly as possible.

The second thing we learned is related to the supply chain. During the pandemic, transportation between countries was almost completely stopped, and most of the raw materials and consumables were being sourced from the USA or Europe. After the experience with COVID-19 vaccine production, the Indian Prime Minister emphasized the importance of being less dependent on other countries for critical supplies. This was one of the biggest issues we faced—the procurement of raw materials and consumables. We have to be very particular about securing all the materials required for both drug substance and drug product manufacturing.

Regulatory collaboration worked well. We have several success stories from the COVID-19 vaccine effort. Even after COVID-19, we have continued with a number of joint ventures and collaborations. Things have improved significantly. Before COVID-19, many companies were working in isolation, handling everything from development to manufacturing on their own. But now things have changed. Most companies prefer to collaborate at different stages and under different business models.

Q How is the vaccine industry in India evolving post-pandemic?

SK In the aftermath of the COVID-19 pandemic, India is well-positioned in terms of scaling up and large-scale manufacturing. The country has built significant capacity, both in terms of drug substance production and drug product manufacturing.

India has long been a global powerhouse in vaccine manufacturing. However, prior to COVID-19, the focus was primarily on traditional platforms such as recombinant, inactivated viral, and bacterial vaccines. During the COVID-19 period, India not only scaled up production but also significantly enhanced its technological capabilities.

Importantly, India has embraced and advanced several new technologies, including mRNA and DNA vaccine platforms, in addition to its existing expertise in recombinant subunit vaccines. Since 2021, India has made substantial progress, not just in manufacturing but also in vaccine development. This positions the country more favorably in the global landscape, particularly concerning innovation in vaccine technologies.

Q There is a lot of discussion currently around expanding vaccine manufacturing in African nations. Do you think that there are lessons to be learned from India's success?

SK There is significant scope for vaccine manufacturing in African countries. A number of discussions are already underway between African governments,

the Developing Countries Vaccine Manufacturers Network (DCVMN), and other stakeholders about establishing in-house or on-site manufacturing capabilities. Some initiatives are already in motion, with efforts being made to set up manufacturing facilities on the continent.

Of course, there will be challenges. Africa has not historically been known for vaccine production, so for many of these countries, it will be a completely new undertaking. In contrast, technology transfer to India has been relatively smooth because there is already a foundational ecosystem and trained workforce in place. In Africa, it may take more effort initially, but challenges are a natural part of growth. Often, only when confronted with challenges do we find the solutions.

I believe the importance of local manufacturing, especially in the context of a pandemic, will become increasingly clear to African nations. With time and with the right support and partnerships, the challenges can be overcome.

Q One approach for African countries could be to focus on newer technologies, such as mRNA. What is your perspective on this?

SK I think that is very possible and practical. If you look at the requirements for setting up facilities and transferring technologies, platforms like mRNA, DNA, or recombinant protein vaccines can be more straightforward than traditional whole-cell, inactivated, or toxoid vaccines. These newer technologies often involve less complex production environments and are easier to standardize.

The key will be for local professionals in Africa to actively engage in capacity-building and training. Every technology comes with its own set of challenges, but with proper guidance and strong collaboration between technology owners and local partners, those challenges can be addressed effectively over time.

Q What do you think are the most important factors in a smooth technology transfer?

SK The most critical elements for a successful technology transfer are openness, continuous communication, and close collaboration between the transferring and receiving teams. A defined timeline and day-to-day interaction are essential.

In many cases, I have observed that technology transfer is treated as a documentation exercise, where the donor simply provides dossiers or technical files. But documentation alone is not sufficient. Practical, hands-on engagement is crucial. On-site collaboration, joint technical work, and ongoing discussions between both parties are vital. While comprehensive documentation is, of course, necessary for regulatory purposes, it cannot replace the value of practical demonstrations and real-time problem-solving.

Another important factor is the evaluation of raw materials and consumables used for developing technology. The materials and consumables used must be assessed against those available locally in the recipient country. Often, variations in raw materials can become bottlenecks, impacting product yield or quality. This evaluation should be integrated into the early stages of technology transfer to avoid disruptions later in the process.

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"Regulatory guidelines and quality standards are becoming increasingly stringent over time."

Today, we are seeing a significant increase in technology transfer activities, and the overall ecosystem has improved, however, the foundation remains the same. Successful technology transfer relies on strong collaboration, regular engagement, and a shared commitment to working through challenges together.

Q What are the main pain points when scaling up vaccine production, and how can these be overcome?

SK One of the aspects we must pay close attention to when scaling up vaccine manufacturing is regulatory compliance. Regulatory guidelines and quality standards are becoming increasingly stringent over time. Vaccines, being administered to healthy individuals, are subject to particularly rigorous scrutiny. At every stage of scale-up or technology transfer, we must demonstrate compliance with quality standards and regulatory requirements.

Another major challenge can arise during the scale-up process, particularly when any modifications occur, such as changes in equipment. If, for instance, equipment used at a larger scale differs from that used in small-scale production, we are required to revisit and revalidate the entire process. Regulatory authorities will not accept a situation where different technologies or processes are used at different stages without thorough validation. Any addition, removal, or alteration of a process step demands comprehensive justification and evidence of maintained quality. To manage this, a scale-down model must be employed and validated meticulously before scale-up. This approach ensures that the scaled-up process mirrors the validated model as closely as possible.

Another significant point relates to equipment specifications; for example, differences in the height-to-diameter ratio of bioreactors used at different scales. Variations like these can introduce complexities, both in process performance and in gaining regulatory approval. Such differences must be addressed with careful process design and robust comparability studies. In general, scale-up in vaccine manufacturing is full of bottlenecks. However, due to the especially strict regulatory landscape in this sector, additional precautions are necessary to ensure compliance and product integrity.

A related trend we are seeing globally is the increasing reliance on collaborations and technology transfers. Rather than traditional scale-up alone, many manufacturers are now engaging in technology transfer, either domestically or internationally. In such cases, the transferred technology must be clearly and comprehensively documented. No deviations from the defined process are acceptable, as regulators require a high degree of consistency and clarity.

Q Is automation something you are looking at?

SK Automation is now an integral part of vaccine manufacturing. We are increasingly moving toward automated systems to reduce human intervention,

particularly in areas where aseptic processing is critical, such as drug product manufacturing. Automation greatly enhances consistency, sterility, and efficiency, and many facilities have already adopted it, or are in the process of transitioning.

That said, the level of ease in implementing automation depends on the age and design of the facility. In newly built plants, incorporating automation is relatively straightforward. These facilities are designed with the latest technologies in mind, and equipment and processes are typically well-integrated and fully synchronized. However, retrofitting older plants presents more challenges. Synchronizing systems with modern automation software can be difficult. Equipment compatibility, process integration, and the reconfiguration of existing workflows often require significant effort and investment.

Another critical aspect is training. As we adopt more advanced automated systems, it becomes essential to ensure that operators on the factory floor are well-trained. They need to understand both how to use the equipment and how to troubleshoot it.

Q What technologies do you think have the most potential for the future?

SK mRNA technology holds significant promise for the future of vaccines. While there are still challenges to address, particularly around the stability of mRNA vaccines, the potential is clear. Currently, most mRNA vaccines require storage at around -20 °C, which complicates distribution, especially in lower-resource settings. However, several companies are actively working on formulations that can remain stable at 2–8 °C, which would greatly ease logistical constraints.

In addition to mRNA, recombinant subunit and protein-based vaccines also show strong potential. These platforms offer flexibility, scalability, and faster development timelines, which are crucial during pandemic scenarios or other public health emergencies. Their manufacturing processes are relatively well-established, making them well-suited for rapid scale-up.

From a safety perspective, both mRNA and recombinant protein technologies are also highly favorable. Unlike traditional vaccines that use whole inactivated viruses or bacteria, these newer platforms carry lower risk profiles, as they do not involve live or inactivated pathogens. This makes them inherently safer for broad population use, including in vulnerable groups.

BIOGRAPHY

Sudeep Kumar is a biopharmaceutical expert with over 28 years of experience in the development and commercialization of recombinant proteins, vaccines, and diagnostic kits. He completed his postdoctoral research in Biotechnology at the University of Valencia, Valencia, Spain and has worked across the entire product lifecycle—from R&D to manufacturing and regulatory approval. Dr Kumar has a strong history of successfully navigating regulatory approvals with agencies such as WHO, US FDA, and SAPRA. He has been deeply involved in the development of novel therapeutics, including therapeutic proteins for cancer treatment, and played a key role in establishing the VLP technology platform for vaccines in India in collaboration with Novavax, USA. He has held senior roles at Ranbaxy, Cadila Pharmaceuticals,

and Unichem. Currently, he serves as Senior Vice President at Biological E Ltd, where he leads traditional and innovative vaccine manufacturing.

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