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Boosting Vaccine Production Needs the Right Degree of Flexibility

The unequal access to Covid-19 vaccines stems from production shortfalls. Building more flexibility into manufacturing processes can help – here's how.

The pandemic has seen an unprecedented global effort to accelerate the development of safe and effective vaccines and a rapid expansion of vaccine manufacturing capacity. However, **challenges in further scaling up vaccine manufacturing capacity** to meet higher-than-expected demand and the resulting inequity in vaccine access have highlighted that our past investments in **building vaccine surge capacity** were insufficient. It is an issue vaccine companies, governments and multilateral agencies must face squarely in order to improve medium-term access to Covid vaccines as well as to gird humanity better against future pandemics.

Recent work has **analysed** financial instruments to expand manufacturing capacity of approved vaccines. But before making decisions about manufacturing, effective vaccines have to be developed. As the race to find Covid-19 vaccines showed us, at the development phase, it is often unclear which platform (mRNA, viral vector and so on) would have the highest likelihood of success in taming a marauding pathogen. Even for currently approved or authorised Covid-19 vaccines, uncertainties abound over the future trajectory of the pandemic and, by extension, that of vaccine manufacturing.

Our best bet, therefore, lies in *flexibility*. Vaccine developers will have to be ready to **modify vaccines to target variants** of the virus that causes Covid-19 and produce sufficient doses quickly. If Covid-19 becomes endemic, variant-matched annual booster shots may be required in the years ahead, and sufficient production will hinge on more flexible manufacturing capacity.

Similarly, any long-term surge capacity as part of the preparedness against future pathogens needs to be flexible enough to pivot from one vaccine manufacturing platform to another. Such flexibility would also contribute to the sustainability of any new manufacturing sites by enabling them to switch to making routine vaccines in between outbreaks.

The tradeoff between cost and flexibility

Vaccines are complex biological products that take **months or even years to make**, from raw materials to packaging. Currently, most large vaccine manufacturing facilities specialise in a single product to achieve economies of scale, but this approach is also highly inflexible: There is no way to quickly switch from making one vaccine to another within the same production plant. While monoclonal antibodies and specialised gene therapy are manufactured using highly flexible manufacturing technology, the facilities are relatively small compared to what is needed for large-scale vaccine production.

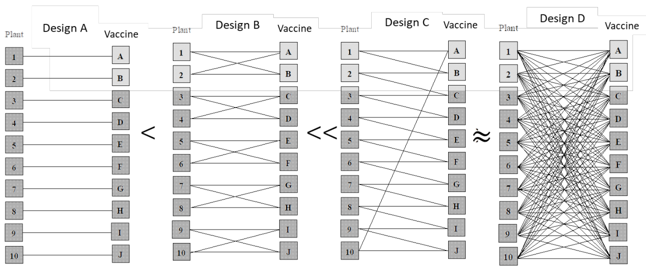
The pandemic has given fresh impetus to process flexibility. Flexible manufacturing entails modular facilities that allow manufacturers to reconfigure equipment such as single-use bioreactors – the apparatus for growing cells under controlled conditions – to accommodate new products or processes.

But flexibility comes at a cost. At large volumes of, say, more than 500 million vaccine doses, flexible manufacturing may not match the economies of scale afforded by dedicated production using large stainless steel or glass vessels/reactors. Indeed, in some instances it may be infeasible due to drastically different operations required for different vaccines.

The design of a vaccine manufacturing network with the *right degree* of flexibility then becomes critically important if we are to maximise global access. Otherwise, low-income countries will continue to get vaccines that are not necessarily the most efficacious against new variants.

A "sparse" design

Designing an optimally flexible vaccine manufacturing network is a matter of mathematical analysis, **which one of us has studied in considerable detail**. The goal is to construct a "sparse" network (Design C in the graphic below) that maximises the expected performance metric for a given type of demand uncertainty in lieu of a fully flexible but often infeasible design (Design D).



Here's a quick explanation. In the graphic, a plant is connected to a vaccine type (e.g. mRNA, viral vector, protein subunit) that it can produce. The challenge is that the network structure of plant-vaccine pairings has to be created in the face of uncertainty, i.e. before the efficacy and resulting demand for each vaccine type becomes clear. Of course, if cost was not an issue, a full-flexibility design would be ideal. But since this would be too costly in practice, the next best solution is often a "sparse" network, i.e. one where the number of edges, or links, is small.

One very useful sparse flexibility design is the *long chain*, depicted by Design C. In such a design, the plant and vaccine nodes are "chained" together: Plant 1 produces vaccine A and B, Plant 2 produces vaccines B and C, and so on. Under **certain common technical conditions**, as one of us found, the long chain is the best sparse design (better than Design B for instance). Although both networks comprise plants that each produces two types of vaccines, C has much higher process flexibility than B.

Additionally, the long chain performs almost as well as the full-flexibility design when demand does not deviate far from average levels. For more routine vaccines, such as pentavalent vaccines for children and perhaps the Covid vaccines given the very high average demand, demand volatility may be low enough for long-chain designs to perform quite well, in which case we can achieve the benefits of flexibility without having to invest in full flexibility. However, it is more difficult to predict demand for vaccines against any future novel pathogens.

It is clear that each firm acting in its own interest cannot always design the most flexible overall network. Coordination by national governments and supranational entities is needed to "nudge" individual companies towards embedding the right degree and right type of flexibility into the manufacturing network.

Embracing uncertainty with flexibility

Flexibility in manufacturing and distribution is not only a physical or engineering feat; it is also about creating nimble decision-making and work processes. Sparse flexibility manufacturing network models can serve as design guidelines and heuristics for capital expenditure and other decisions in the building of new vaccine plants. They can also benefit processes in vaccine sourcing and distribution.

Should each transport leg and warehouse be designed to handle every type of vaccine with varying temperature and storage requirements, or should there be dedicated warehouses (or special rooms within warehouses) for some types of vaccines? Conundrums like these will bring us back to the tradeoff between flexibility and cost-efficiency again and again. While we work to solve the exact problem of designing a flexible vaccine supply network to best meet societal needs, the analysis described above can be a reliable guide to negotiating the optimal balance.

__Prashant Yadav__ is an Affiliate Professor of Technology and Operations Management at INSEAD and the Academic Director of the __INSEAD Africa Initiative__. His work focuses on improving healthcare supply chains and designing better supply chains for *products with social benefits.*

Antoine Désir *is an Assistant Professor of Technology and Operations Management at INSEAD. His research focuses on developing efficient data-driven algorithms for revenue management and improving the design of online marketplaces.*

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