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VACCINE INSIGHTS

SPOTLIGHT

Sustainability in vaccine development and production

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SUSTAINABILITY IN VACCINE DEVELOPMENT AND PRODUCTION

SPOTLIGHT

COMMENTARY

Pioneering technological innovation and sustainability in vaccine manufacturing to ensure pandemic preparedness and global access

Anca Tacu, Martina Micheletti, Stephen A Morris, and Brenda Parker

The COVID-19 pandemic demonstrated the potential of accelerated vaccine development and manufacturing but also exposed systemic weaknesses in global preparedness and equitable access. Today, with the world still at risk of new pandemics exacerbated by climate change, there is an urgent need to reimagine vaccine manufacturing through the dual lenses of technological innovation and environmental sustainability. In this article, we explore key enablers for minimizing waste and embedding circular economy thinking into vaccine research and production. We discuss VaxHub Sustainable as an example of how to integrate multidisciplinary expertise to support vaccine technology innovation and minimize the environmental footprint of vaccine manufacturing. By aligning pandemic preparedness with sustainable bioprocess design, this work aims to ensure resilient vaccine manufacturing for the future.

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Vaccines are one of the most important tools we have in promoting global health and wellbeing. A recent report estimates that in the last 50 years over 150 million lives (six lives every minute), of which 101 million have been infants, have been saved by the WHO Expanded Programme on Immunization, launched in 1974 [1]. During the COVID-19 pandemic, vaccines are estimated to have saved over 20 million lives worldwide [2]. While vaccine development has historically taken decades, the recent development, manufacturing and deployment worldwide of COVID vaccines within 18 months demonstrated that this can be achieved more quickly—but at a large financial cost. The Independent Panel, co-chaired by the RH Helen Clark and HE Ellen Johnson Sirleaf, that reviewed the global COVID-19 response found weak links at every point of the chain of preparedness and response, and concluded

that major losses could be prevented by sustained domestic investment in public health [3]. The WHO have highlighted a list of pathogens that should be monitored for their epidemic potential [4] and we remain at risk of new pandemics, e.g., H5N1 and mpox. Meanwhile, a recent report highlighted that the world is still in many ways unprepared [3].

In the case of seasonal influenza vaccine, manufacturing capacity has remained relatively constant over the last 5 years, at around 1.53 billion doses [5]. Despite the need for global access, the Global Vaccine Market Report [6] found that just ten manufacturers were supplying 75% of total vaccines doses (excluding COVID-19), with the rest being manufactured by more than 80 stakeholders. The vast majority of vaccines required by the African and Eastern Mediterranean regions continue to come from outside these areas. This has led to increasing calls for initiatives to establish and support more regional development and manufacturing. Such initiatives include the establishment of the Regionalized Vaccine Manufacturing Collaborative formed by the World Economic Forum, the regional manufacturing strategy by GAVI and the mRNA Technology Transfer Programme sponsored by the WHO.

COVID vaccines relied heavily on new technologies in which the UK had a leading role, especially the development of the adenoviral vector systems used by the Oxford-AstraZeneca collaboration. Moving forward, however, will require significant research on a broader range of technologies. To enable the UK and the world to be better prepared for the next pandemic and improve and support local manufacturing, initiatives could focus on:

- De-risking manufacture of new vaccines by strategically innovating for a selected range of the most promising platform technologies (established and novel/disruptive);
- Developing manufacturing options that improve the product quality and so immunogenicity;
- Streamlining manufacturing process development with novel responsive solutions and advanced digitalization strategies;
- Enhancing stability and needle-free administration routes.

In addition, given the increased risks posed by climate change and wider sustainability challenges, initiatives to improve both the economic and environmental sustainability of vaccine manufacturing and supply will be essential. The vision of initiatives like EPSRC-funded Manufacturing Research Hub for a Sustainable Future (VaxHub Sustainable) is to embed sustainability in research objectives as well as in operations, all designed to minimize environmental impact and carbon emissions, while maximizing use of resources and decreasing waste. VaxHub Sustainable brings together a multidisciplinary team of leading researchers with decades of cumulative experience in all aspects of vaccine design and manufacturing research, as well as industry scientists and policymakers, to propose radical change in vaccine development and manufacturing technologies.

THE UK POLICY LANDSCAPE

The adoption at scale of sustainability-focused innovations in the vaccine manufacturing sector requires a joined-up policy approach across multiple areas including infrastructure, cross-sectoral knowledge sharing, regulation and standards, which address existing barriers whilst creating incentives that accelerate such innovations. The **UK Industrial Strategy**, as well as the **upcoming Circular Economy Strategy for England**, present

clear opportunities for the UK government to set out its long-term vision and the policy mechanisms to drive investment in technologies that enable sustainability and resource circularity. At an international level, other countries have committed to ambitious goals for harnessing the potential of such technologies, with the European Commission launching a Biotech and Biomanufacturing Hub as part of its strategy to boost biotechnology and biomanufacturing in the EU [7].

A key element of advancing sustainability in vaccine manufacturing, and in the life sciences sector more broadly, is the facilitation of close collaborations between academia, industry and policymakers [8], which is a key pillar of the work of VaxHub Sustainable. Collaboration is also important across the supply chain, including with other sectors such as clean energy and digital technologies. Government action can help to create a robust innovation ecosystem by fostering knowledge sharing and cross-sectoral collaborations on net-zero and wider sustainability challenges [9,10]. An illustrative example is the Sustainable Medicines Manufacturing Innovation Programme, led by Innovate UK, which focuses on enhancing the UK's pharmaceutical manufacturing innovation ecosystem and promoting sustainable practices.

The pharmaceutical industry is highly regulated due to the importance of ensuring the safety and efficacy of its products, including vaccines. At the same time, regulatory standards can act as a barrier when it comes to increasing the sustainability of vaccines [9]. For example, it is challenging to change manufacturing processes to meet sustainability goals once they have been approved as meeting GMP standards [11]. If regulation is to support the adoption of sustainability-focused changes across the pharmaceutical industry, a more proactively enabling approach is required; more specifically, the assessment of new products by the regulator could include sustainability as a criterion, alongside quality, efficacy, and safety [12]. This would also require having an agreed framework that clearly articulates which sustainability-related factors should be measured and what data should be collected and reported. Any such framework would also be dependent on having a common language for bioprocess development, similar to the minimum information standards developed for biosciences [9]. The recently created Regulation Innovation Office focuses on engineering biology as a key emerging technology and could be well-placed to incentivize innovations geared towards sustainability in vaccine manufacturing through targeted regulatory reform.

Common standards and metrics have an equally essential role in supporting innovation in sustainable vaccine manufacturing. There is currently a lack of unified methods, data systems, and metrics for measuring and communicating the environmental impact of medicine manufacturing, which has led to fragmentation and different stakeholders using different sustainability targets [9,13]. The UK Government could provide leadership and enable the adoption of sustainability measurements and standards by building on existing initiatives like the BSI Environmental Impact of Pharmaceutical Standards Hub, which is aiming to build consensus on a method for assessing the environmental impact of medicines.

ENVIRONMENTAL IMPACT TOOLBOX & WASTE REDUCTION

Although the pharmaceutical industry is a significant contributor to greenhouse gas emissions (GHG) [14], this has not been researched to the same extent as in the case of other industries [15]. When compared to other industries, there is also a notable lack of low-carbon pharmaceutical products [9,16]. One of the challenges is that claims of sustainability for bioprocesses need to be substantiated with evidence.

Life Cycle Assessment (LCA) tools are currently being implemented at all stages of the manufacturing supply chain, and there are pressures on suppliers to provide data on sustainability impacts. The ISO standard specifies four steps to conduct any LCA: goal and scope definition, life cycle inventory, life cycle impact assessment, and interpretation. The system boundary is defined upfront and determines what is counted when evaluating footprint. Drawing this boundary in a fair manner to be able to compare new manufacturing systems side-by-side requires knowledge of the wider production workflow to prevent discounting of impacts that lie outside of the factory gate [17]. For instance, cell-free synthesis still relies on production of enzymes, which requires associated fermentation-based resource. Converting inventory data to impact assessments relies on LCA databases that have relatively few of the key ingredients used in vaccine manufacturing: media components, buffers and also materials used for single-use equipment. This makes translating inventory data into process impacts rather cumbersome, and relies on calculating this from scratch, or making substitutions that can be a source of inaccuracy. Conjoint efforts to contribute to databases such as EcoInvent will increase the ability of the field to produce consistent LCA information. Biological manufacturing has a number of aspects that are distinct from chemical synthesis; notably, process variability and the generation of biogenic carbon. Within the sector we need thought leadership to harmonize how these factors are considered. After the impact assessment, while carbon is a primary focus of—due to net zero pressures—it is vital that this is not the sole criteria that is used for decision making. Solutions that drive down carbon can have unintended consequences; for example, driving up land use change or other emissions or reducing the lifespan of the components. Therefore, sustainability must be considered in a truly holistic manner. For emerging production systems, the ability to perform *ex ante* LCA enables developers to leverage the design freedom to embed sustainability at an early stage, where the greatest gains can be made while navigating considerable uncertainty [18]. Decision-making in sustainability is surprisingly complex, and to facilitate good choices requires a fluency in LCA amongst members of the industry, and clearer mechanisms to communicate the trade-offs between options.

One innovative approach could be to consider vaccine manufacturing as part of industrial ecology, which involves systemically considering the relationships between society, the economy, and the natural environment. Within this framework, the circular economy has been an umbrella concept [19] to describe techniques for prolonging resource utilization by understanding the mass and energy flows of a system. By considering opportunities for reuse, recycling, and remanufacturing the industry can minimize waste. Yet the biopharma industry, including the vaccine manufacturing space, has not been a visible participant due to tight regulations, concerns about release of genetically modified organisms or lack of compatible solutions.

The view that the 'polluter pays' is a key principle behind EU environmental policy. Biotechnology at scale, especially bioprocesses that rely on substantial purification strategies, inevitably generate substantial aqueous waste streams. Recycling through membranes is a potential option, but this has implications on brine generation and energy consumption that must be balanced [20]. Alternatively, industrial symbiosis is one approach where value can be derived from spent materials by cascading waste streams through activities that share requirements for specific inputs. There are few examples of this at scale, but Kalundborg Symbiosis in Zealand,

Denmark has several biotech participants [21] who receive steam, share treated surface water, produce biogas from spent biomass after enzyme manufacturing, and supply surplus heat to district heating schemes. The demonstrable success of Kalundborg illustrates the importance of the carbon-water nexus. Activating networks such as this involve entities outside the company framework and creating trusted partnerships. As aforementioned, an engaged network, comprising stakeholders from the sector (academia, industry, policy makers, and other organizations worldwide), is vital to ensure technological innovation while minimizing environmental impact.

Design of integrated solutions for resource management also enables companies to achieve insetting, as opposed to offsetting, of emissions, where the facility itself is an important place to begin. Viewing the manufacturing site itself as having the capacity to remediate, or participate in ecological cycles, is an opportunity for innovative design and the creation of green infrastructure [22]. Understanding which loops can potentially create a relationship between inner and outer parts of the building offers the potential for creative thinking about potential allied industries that could operate in symbiosis to a manufacturing site. This will require a mapping of available waste streams, and the development of compatible technologies that are able to work in synergy with the scale of operation.

NEXT STEPS

The recent pandemic and the frequency and extent of epidemic episodes worldwide has put pressures on governments for sustained investment in vaccine manufacturing, especially focusing on new vaccine technologies that have proven the most successful in an emergency scenario. Given the multi-disciplinarity and complexity of some of the challenges in the sector (i.e., vaccine immunogenicity, process and analytical development, thermostability) the additional question of quantifying and minimizing environmental impact needs a coordinated approach, as well as appropriate methodologies and standards. While the current framework for LCA methodology (ISO standard) provides a general template, producing life cycle assessments that are comparable is challenging. Similarly, the current LCA databases are not comprehensive in regard to the types of inputs relevant to biotechnological manufacturing, for example media formulation, or single-use consumables. On the other hand, while quantitative assessments are crucial for hotspot analysis and decision-making, it would be interesting to plan for facilities to be embedded within a circular economy and aim to address key aspects around the use of waste and novel facility design, in particular if regulatory constraints make any substantial bioprocess changes prohibitive. Future plans might include considerations of the impact of single-use equipment, use of which is increasingly widespread within the biopharmaceutical manufacturing industry, as well as solutions towards process intensification.

Knowledge transfer from VaxHub Sustainable points towards a more integrated process design methodology based on exchanges between biological and engineering approaches, supported by continual technological innovation. In the short term, this can be enabled by increasing literacy in the field of sustainability. Ultimately, this aligns with a triple bottom line to minimize resource consumption, which has clear economic incentives. As future facilities for pandemic preparedness are constructed globally, there is a window of opportunity to embed inherently sustainable design at all stages, becoming an exemplar for other bioprocesses.

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AUTHORSHIP & CONFLICT OF INTEREST

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SUSTAINABILITY IN VACCINE DEVELOPMENT AND PRODUCTION

SPOTLIGHT

Key considerations around the decision to localize vaccine manufacture in LMIC countries

INTERVIEW

"...we will see some more LMIC manufacturers coming to market in the fairly near future, and becoming a fixture of the global vaccine supply chain in the years to come."

Charlotte Barker, Commissioning Editor, *Vaccine Insights*, talks to **Kristopher Howard**, Managing Director/Owner, NRL Enterprise Solutions, about learnings gleaned from a career spent establishing vaccine manufacturing facilities and conducting tech transfer around the world.

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Q Tell us about your background and interests

KH I have been in the industry for just over 20 years. I started out with Merck Sharp & Dohme (MSD), designing and building manufacturing facilities. I worked for a short period on a pharmaceutical API facility before moving into vaccines, where I remained for almost a decade. Initially, I designed and built MSD facilities and then tech transferred vaccines to those from other MSD facilities. However, towards the end of my time at MSD, I became involved in tech transfers to partners in low- and

middle-income countries (LMIC) such as Brazil, Argentina, Russia, and Egypt. I was engaged in finding partners and setting up deals in those countries for MSD.

I left MSD 12 years ago and became an independent consultant. I always enjoyed working with the smaller companies in LMICs and decided to make that a focus of my consultancy work. Over the years, I have written white papers on vaccine manufacturing in LMICs for the United Nations Industrial Development Organization (UNIDO) and the WHO, and supported companies in Serbia and several African nations prior to the COVID-19 pandemic. Following the pandemic, my work in LMICs really took off. During the early part of the pandemic, I worked for various stakeholders including development banks such as Asian Development Bank and Inter-American Development Bank. I was also seconded to Africa CDC and became involved in their Partnership for African Vaccine Manufacturing (PAVM).

Q What are you working on right now?

KH Most of my work is focused on Africa. My two current clients are the Regionalized Vaccine Manufacturing Collaborative (RVMC) and the Gates Foundation—with them, I look to see how we can help African vaccine manufacturers to initially get up to scale and become capable of bringing their products to market. A lot of it is helping them to develop a stable operating platform in terms of products on the market and good production volumes to ensure their long-term viability.

Q What are the greatest technical, infrastructure, and financial barriers for governments and investors wanting to establish or expand vaccine manufacturing capability in LMIC?

KH I recently wrote a **series of articles** on LinkedIn on this very topic. I approached it mainly from the government standpoint because I think the biggest barriers for companies are generally well understood: vaccines are a scale business with tight margins, particularly in LMIC where margins can be an order of magnitude lower than they are in high-income countries. So for the vaccine industry, it's chiefly about establishing a marketplace, ensuring reasonable demand and uptake, and having the know-how and the infrastructure to be able to deliver at scale.

Typically, the more significant hurdles and greater information asymmetry lies with governments that are trying to support a vaccine manufacturing capability for the first time, especially in this post-COVID-19 world. During and following the pandemic, many LMIC government decision-makers found themselves squarely in the headlights, so to speak, having to make decisions around vaccine procurement and vaccine infrastructure within their countries, with just months to figure out strategies that other nations had taken decades to perfect.

Simply conveying the necessary information to those stakeholders remains a key priority, not least because many of the decision-makers involved don't have a vaccine industry background and much of the knowledge they require is not available in the public domain.

The vaccine industry is highly competitive and doesn't operate in the same way as other industries do. For example, LMIC countries are often reliant on technology transfers

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"There are also often unrealistic expectations around the time it takes to set up a vaccine manufacturing facility."

from their current suppliers, and they sometimes put too much onus on the outcomes of feasibility studies conducted by third parties, thinking that a positive feasibility study will allow them to move forward. But the unfortunate reality is that not enough feasibility studies fail. If you work for a multinational company, there will be many projects that fail at a feasibility study level, and you just drop them and move on. However, that doesn't always happen in other environments.

The vaccine industry and the pharma industry may be cousins, but they are not the same. There are some key differences that need to be understood in order to successfully navigate the vaccines industry.

Q Can you expand on these differences?

KH The markets are totally different. Firstly, the pharma market by value is at least an order of magnitude larger than the vaccine market and it's a much more diverse group of purchasers. The government is a pharma purchaser, but they are usually not the biggest purchaser in the country because you also have private markets and in some cases, donors. You are catering both to the health insurance companies and to those individuals who are paying out of pocket because they have no health insurance. Therefore, it is much more diverse group of purchasers compared to vaccines. It is the government or donors that buy the overwhelming majority of the vaccines, which they distribute through their immunization program. That fact obviously plays a major role in how deals are structured.

Secondly, the global vaccine industry is much smaller in terms of both the number of players and products, which means that the nature of the competition is different. Taking India as an example, there are thousands of pharmaceutical manufacturers in the country. This makes the decision of which one to choose for a tech transfer enormously complex—the possibilities are practically endless. But if I want to make a pneumococcal conjugate vaccine (PCV), for example, there are perhaps five manufacturers globally with WHO PQ—and for some vaccine products, there is only a single manufacturer. If you want to do a tech transfer, you need to convince that one manufacturer not to be 100% competitive—that you can still compete in some ways, but you also want to partner with them. It's a very different market dynamic from that perspective as well.

Thirdly, small molecule drugs are typically easier to manufacture than biologicals like vaccines.

Q What were some of the other barriers for LMICs that want to build vaccine manufacturing infrastructure?

KH There is a lengthy timeline from R&D to drug substance to drug product. Stakeholders often want to do everything, but that is often unrealistic—they

"So much depends on the cost at which you can produce the vaccine…"

may need to pick one to begin with and then look to grow into the entire life cycle. There are also often unrealistic expectations around the time it takes to set up a vaccine manufacturing facility.

Cost and pricing are another major barrier. So much depends on the cost at which you can produce the vaccine, but there is very little information in the public domain about this aspect. In my soon to be published article, I have provided a few mental models to help stakeholders to understand fundamentals such as whether their price is going to go in the right direction, or how they can be competitive. A few basic rules they can use to size up an opportunity and its cost implications—to gain a better picture of what a certain deal structure or partnership could ultimately look like.

Q What are some of the success stories you've seen in this area? And are there any cautionary tales you can share?

KH I have certainly seen both! I think all of the success stories—the approaches that have worked—are a function of the point in history and the ecosystem in which they took place. For example, Indian vaccine manufacturers grew dramatically in a time and place that was unique, in parallel with the advent of UNICEF and then Gavi, which created so much opportunity for them.

We are not living in that same world anymore. There has been a consolidation in demand, and the market is now very price-driven. However, there is also renewed interest in localizing manufacturing after the COVID-19 pandemic. Today, there is a different set of opportunities and strengths, of tailwinds and headwinds, which companies and countries can use to their advantage or that may impede their progress.

It's difficult to say which of the new approaches to follow, but one of the things that seems to be a constant is that vaccine manufacturing is a scale business. Just like any other manufacturing, you have to hit a certain economy of scale to be able to be price-competitive. The advent of new production platforms will enable lower volumes to be price-competitive with older platforms, but competitors will eventually have that same advantage as well. Another thing that is guaranteed to change over time is the market dynamics—who is willing to ringfence certain portions of demand and what price they are willing to pay. I would say that people in LMICs are more willing to pay a price premium for locally made vaccines now than they were pre-COVID-19 because they have seen the value of having vaccine manufacturing capabilities. But the underlying finances and technology remain broadly the same, while I would argue that the environment and ecosystem have changed at a faster pace over the past 5 years.

In terms of success stories and cautionary tales, there were great successes and some spectacular failures in COVID-19 vaccine tech transfer projects. But probably the greatest success story I can point to over the past few decades is simply the rise of developing country vaccine manufacturers in terms of their ability to increase global vaccine access and public health outcomes. Gavi has spoken at length about how they have been able to diversify their supply portfolio, increase access, and ultimately get more people around the world immunized.

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In recent years, two particular success stories stand out for me. The first is Gavi raising US$1.2 billion for their African Vaccine Manufacturing Accelerator (AVMA). This is a 10-year program that is essentially designed to help African vaccine manufacturers close the gap in the prices they offer versus incumbent vaccine manufacturers, so that they can get up to scale and be more competitive in the global vaccine marketplace over time.

The second example is a tech transfer deal that was done recently between the Pan American Health Organization (PAHO), Sinergium (a vaccine company based in Argentina), and Pfizer for PCV20. This is interesting because it is a rare example of a tech transfer deal that is intended to provide a routine vaccine through a local manufacturer for an entire region rather than an individual country. In the past, these tech transfer deals to localize manufacturing were done with individual countries—Brazil have done several. But if the vaccine was being made in Brazil by a local manufacturer, it would be strictly for the Brazilian market—there would be no possibility of exporting the vaccine product to other countries in need. As far as I'm aware, this was the first time multiple stakeholders came together and negotiated a deal to cover regional demand for a non-pandemic vaccine. I think this type of deal could prove to be increasingly enticing for all actors involved, in addition to the country-by-country approach.

I've been working in Africa, supporting the ecosystem where there are a number of projects. It would be great if we could get more of those regional or continental deals happening in Africa. There have now been 8–10 tech transfers announced there, but building the requisite demand remains an ongoing process.

As part of my work with Africa CDC, and along with CHAI and PATH, I led site visits to African vaccine manufacturing facilities that allowed us to landscape all of the manufacturers, capacity, and tech transfer deals on the continent, including all of the vaccines that are likely to come to market in the next 5 years. We now have a list of vaccines that are being tech transferred, and manufacturers are currently ascertaining the route to commercialization for them—what kind of demand they can expect, and what mechanisms they need to work through to meet it. It is a big undertaking, not least because they are trying to move all 8-10 tech transfers in a relatively short period of time.

Q How do you see vaccine manufacturing in LMIC evolving over time?

KH The COVID-19 pandemic set us on a trajectory where regionalized or local vaccine manufacturing within LMIC countries seems likely to continue. We are seeing a lot of political will in that direction and money is being invested, but as sovereign nations, these countries retain the ability to choose where to put their money, whether it is to establish local manufacturing or to import the vaccines. I think that picture will continue to develop, although how it will pan out will vary from country to country and even company to company.

From working with the various vaccine manufacturers in Africa, I can see that they are all taking slightly different paths. That is largely predicated on their own structure: are they part of a larger organization? Are they solely focused on vaccines? Are they public or private entities? I think each of them will continue to work their way through the ecosystem based on their relative strengths and resources, and it is difficult to predict how that will turn out for each individual company. However, I will say that there has been

enough sustained momentum to make me believe that we will see some more LMIC manufacturers coming to market in the fairly near future, and becoming a fixture of the global vaccine supply chain in the years to come. I think that will happen in Africa and Latin America, and it will certainly continue to happen in Asia. It will be interesting to see what that means for the incumbent manufacturers.

Q Do you have any parting advice for governments and companies working to expand localization of vaccine manufacturing in LMIC?

KH The main thing is to realize that the vaccine industry is complex, but that there is a lot of information out there about it. Seeking a wide range of opinions and expert input is definitely worth the effort, especially if you are planning to spend hundreds of millions of dollars setting up a new facility. My greatest concern is that a country thinks that it can set up a new vaccine manufacturing facility for $150 million and decrease the cost of the vaccines it makes. Then a few years down the line, they find they have spent $75 million, the facility is actually going to cost $300 million, and the vaccines are going to be twice as expensive as they initially believed. At a time when public health spending is under pressure globally, an investment of hundreds of millions of dollars that doesn't meet its initial objectives is just not something we can absorb anymore.

If you're going to spend millions of dollars, it is critical to do your due diligence and, crucially, be willing to kill a project early if your research shows that it doesn't make financial sense.

The author's series of articles can be found on **LinkedIn**.

BIOGRAPHY

For over 20 years, **Kristopher Howard** has helped clients such as Merck, Sharp and Dohme (MSD), InterAmerican Development Bank, the WHO, Africa Centers for Disease Control, and others to evaluate, develop, and implement plans to sustainably manufacture life-saving vaccines in Low and Middle-Income Countries (LMICs). Kris works with countries, funders, and manufacturers to bring the clarity needed to confidently navigate the decisions and challenges faced while establishing or expanding local vaccine manufacturing in LMICs. He has worked extensively in Africa, Latin America, the USA, and Europe and regularly works with governments and the leading global health stakeholders. In his former role at Merck & Co. Inc. (MSD), Kris evaluated and implemented local vaccine and pharma technology transfer deals in LMIC countries to facilitate MSD's global expansion plans. Prior to this, he was part of MSD's team responsible for designing, constructing, starting up, and optimizing production facilities around the world. Kris holds a degree in Chemical Engineering from Carnegie Mellon University. Although he is originally from the USA, he has lived in various European countries since 2007. Kris currently lives in Ireland with his wife Theresa and his children Ronan, Oisin, and Niamh.

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AUTHORSHIP & CONFLICT OF INTEREST

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VACCINE INSIGHTS

SUSTAINABILITY IN VACCINE DEVELOPMENT AND PRODUCTION

SPOTLIGHT

REVIEW

Building long-term vaccine manufacturing capacity for the world: a framework for sustainable development in LMICs

Salomé De Sá Magalhães and Eli Keshavarz-Moore

The recent global pandemic has put in the spotlight the urgent need for low- and middle-income countries (LMICs) to develop sustainable vaccine manufacturing capacity to ensure equitable access to life-saving vaccines in future health crises. This paper reviews current practices and highlights an informed framework for building long-term vaccine manufacturing capacity in LMICs, emphasizing the importance of local, regional, and global cooperation. Key recommendations include strengthening domestic leadership and technical training, creating a workable locally achievable regulatory environment, fostering public–private partnerships. Additionally, the framework outlines a phased approach to capacity building, with immediate priorities focused on infrastructure and technology transfer, followed by medium-term goals of scaling production and ensuring self-sufficiency. The paper also proposes metrics for success, including the number of doses produced locally, the percentage of vaccines procured from LMIC manufacturers, and the speed of vaccine development during outbreaks. The framework aims to empower LMICs to lead in vaccine production, reducing dependency on high-income countries and promoting a more equitable, resilient global health system.

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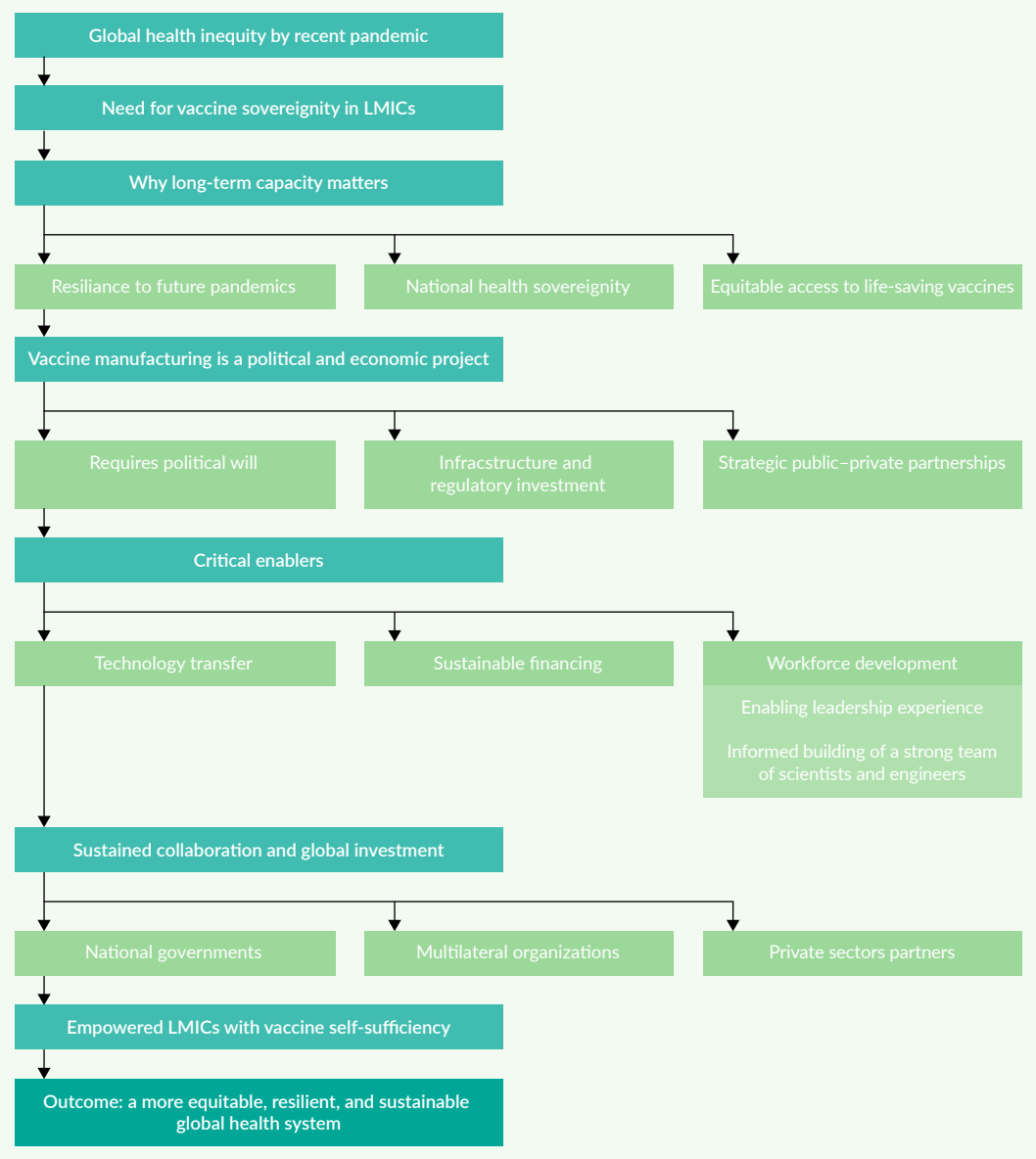
INTRODUCTION

Importance of global vaccine equity and the need for distributed manufacturing

Global vaccine equity refers to the fair and equitable distribution of vaccines across all nations, regardless of their economic status. This principle is vital not only from an ethical standpoint but also for effective pandemic control and global health security. During the COVID-19 pandemic, disparities in vaccine access led to prolonged outbreaks in low- and middle-income countries (LMICs), allowing viral mutations



Graphical abstract. Powering global health from the ground up: a visual journey through the pillars of sustainable vaccine manufacturing in LMICs.

to occur and increasing the risk of global transmission. As of late 2021, for example, more than 70% of people in high-income countries had received at least one vaccine dose, compared to just 4% in low-income countries [1,2]. However, to better understand the needs for vaccine supply and production it is worthwhile reviewing the definition of what is meant by low or middle-income countries. According to the World Bank, there has been some significant shifts in reclassification of certain countries/regions since the late 1980s, with some regions (e.g., South Asia) reducing their share of low-income to only 13%. [3]. It is therefore difficult to consider that the same policies and recommendations would be applicable to all countries that may fall under one or other categories. But one certainty is in that irrespective of location or wealth, there is a global need for vaccines either during a crisis (pandemic or endemic) or as insurance against such surges.

The COVID-19 pandemic exposed critical vulnerabilities in the global vaccine

manufacturing landscape, particularly in low- and middle-income countries (LMICs), where limited infrastructure, supply chain dependencies, and insufficient policy support hindered timely access to life-saving vaccines [2,4]. In response, there has been growing momentum to localize vaccine production in LMICs to improve regional self-sufficiency, reduce reliance on external suppliers, and enhance pandemic preparedness. This manuscript explores the strategic considerations for building long-term, sustainable vaccine manufacturing capacity in LMICs, including the optimal number, size, and type of facilities, as well as the local, continental, and global policy interventions needed to support these efforts.

While the primary focus of this study is on low- and middle-income countries (LMICs), it is essential to acknowledge that high-income countries (HICs) also faced notable constraints in vaccine manufacturing during the COVID-19 pandemic. Despite their advanced healthcare infrastructure and financial resources, several HICs, including Canada, Australia, Japan, and the Netherlands, lacked sufficient domestic vaccine production capacity and were consequently dependent on international supply chains to secure vaccine doses [5].

Canada, for example, had limited domestic biomanufacturing capabilities at the onset of the pandemic and was compelled to rely on imports from countries such as India and the United States to meet its vaccination needs [5,6]. Similarly, Australia initially depended on imported vaccines before scaling up local production of the AstraZeneca vaccine, underscoring the vulnerability of even well-resourced nations to global supply chain disruptions [6,7]. Japan and the Netherlands also experienced delays in vaccine rollout due to their reliance on external manufacturing sources [8].

These challenges highlight a broader systemic issue: the global concentration of vaccine manufacturing in a limited number of countries created bottlenecks that affected both LMICs and HICs. The World Health Organization (WHO) has emphasized that equitable access to vaccines requires not only dose sharing but also the decentralization and expansion of manufacturing capabilities worldwide [6]. Strengthening regional production hubs and investing in end-to-end vaccine development infrastructure are now recognized as critical strategies to enhance global pandemic preparedness and resilience [5].

This reliance exposed vulnerabilities in global supply chains and highlighted the need for broader investment in manufacturing infrastructure, technology transfer, and policy coordination across all income levels. The pandemic demonstrated that vaccine equity and preparedness are global issues, not confined to LMICs alone. Strengthening regional and global collaboration, including among HICs, will be essential to ensure a resilient and inclusive vaccine manufacturing ecosystem for future health emergencies [7,9].

Challenges in vaccination in LMICs

LMICs entered the pandemic with limited healthcare infrastructure, high dependency on imports, and insufficient manufacturing capabilities. The resulting supply chain disruptions led to critical shortages of medicines and equipment, particularly in regions like sub-Saharan Africa [10]. The closure of borders, reduced air traffic, and delays in international aid further deepened the crisis.

The growing focus on localized vaccine manufacturing in low- and middle-income countries (LMICs) is seen as a vital strategy to enhance global health equity, lessen reliance on high-income nations, and improve regional preparedness for future pandemics. By producing vaccines locally, LMICs can reduce vulnerabilities associated with global supply chain disruptions, ensure more equal access to essential vaccines, and strengthen healthcare systems. Additionally, local manufacturing can

drive economic growth, generate employment, and alleviate the financial burden of depending on foreign suppliers. However, despite these significant advantages, several key challenges hinder the effective scaling of vaccine production in these regions [11].

Skilled workforce and training gaps

A central challenge in establishing vaccine manufacturing capabilities in LMICs is the lack of a sufficiently skilled workforce. The production of vaccines is a complex, technology-driven process that requires expertise in various fields such as biotechnology, microbiology, engineering, and quality assurance. Strong leadership capability and specialized knowledge and skills required to run vaccine production facilities are often in short supply in many LMICs due to deficiencies in educational infrastructure, limited access to advanced training, and the outflow of talent to higher-paying positions in developed countries. As a result, these countries struggle to develop a competent workforce capable of supporting the advanced manufacturing processes needed for large-scale vaccine production, this includes gaps in technical expertise, quality assurance, and bioprocess engineering, skills that are essential for operating and scaling vaccine production facilities. While not the only challenge, we maintain that workforce limitations are a critical constraint, particularly when combined with limited access to advanced training programs and retention issues due to brain drain [12,13]. According to a study by the WHO, fewer than 30% of the national regulatory authorities (NRAs) in LMICs have the necessary capacity to regulate the production of medical products, including vaccines, effectively [2]. This further exacerbates the situation, as a lack of skilled personnel delays production timelines, affects product quality, and hampers national vaccine manufacturing initiatives [5,14].

Regulatory hurdles

Regulatory challenges present another significant barrier to the scaling of vaccine manufacturing in LMICs. Several countries in these regions lack well-established and fully functional regulatory systems, which are necessary to ensure the safety, efficacy, and quality of vaccines. The WHO's prequalification process, which is required for vaccines to be approved for international distribution, can be lengthy, costly, and difficult for LMICs to navigate. A lack of harmonized regulatory standards between countries further complicates vaccine approval, particularly when vaccines must undergo multiple evaluations across different national regulatory bodies. For instance, although there has been progress in some regions, such as the African Union's efforts to enhance local vaccine production capabilities, only a small proportion of African countries have regulatory systems that meet the WHO's standards for vaccine quality assurance. This delay in regulatory capacity often leads to the slow approval of vaccines and can prevent LMICs from benefiting from the global vaccine market or protecting their populations from vaccine-preventable diseases in a timely manner. Regulatory capacity refers not only to the existence of national regulatory authorities (NRAs) but also to their ability to meet international standards for vaccine approval, quality control, and pharmacovigilance. In many LMICs, NRAs are under-resourced or lack WHO maturity level 3 or 4 status, which can delay local production and international distribution. Strengthening regulatory systems is therefore essential for enabling timely and safe vaccine manufacturing, strengthening the capacity of regulatory authorities through international collaboration and training is essential to overcoming these hurdles and ensuring that locally produced vaccines meet global standards [15–18].

Market demand predictability and procurement assurance

A third major challenge is the unpredictable nature of vaccine demand and the uncertainty surrounding procurement processes. Without long-term, reliable procurement agreements and purchasing commitments, local manufacturers face significant risks. For instance, if manufacturers are unable to predict the demand for vaccines with accuracy, they may face either overproduction or shortages. This can lead to inefficiencies, wasted resources, and financial losses, which deter private investment in vaccine manufacturing in LMICs. Additionally, without strong procurement guarantees, manufacturers may be hesitant to invest in infrastructure and technology upgrades necessary for scaling up production.

The unpredictability of vaccine demand is further compounded by the fact that many LMICs rely on international organizations such as Gavi and UNICEF for vaccine procurement and distribution. While these organizations play a critical role in ensuring global access to vaccines, their funding and distribution strategies may not always align with the specific needs or timelines of local manufacturers. In some cases, the delay in procurement decisions and the lack of clear market signals have left manufacturers with unsold vaccines, undermining their economic sustainability. Securing long-term commitments and creating predictable, transparent vaccine markets is essential to building local manufacturing capacity and encouraging investment in this sector [14,19].

Cost and financing constraints

Finally, one of the most significant barriers to establishing and scaling up vaccine manufacturing in LMICs is the high cost of building and operating production facilities. The initial capital investment required for establishing a vaccine manufacturing plant, including the costs of purchasing equipment, facilities, and raw materials, is substantial. Moreover, ongoing operational costs, including those related to quality control, workforce maintenance, and raw material sourcing, are also considerable. Many LMICs struggle to secure the necessary financing to cover these costs due to limited access to capital markets, donor fatigue, and the absence of sustained financial support from international partners.

A recent study estimates that LMICs face a funding gap of US$ 38.4 billion for vaccine acquisition and delivery between 2011 and 2030. This financial shortfall highlights the challenge of ensuring sustainable vaccine production and delivery in low-income countries. Innovative financing models, such as public-private partnerships, foreign direct investment, and international grants, will be key to addressing this gap and enabling LMICs to build and sustain their own vaccine manufacturing capabilities. Additionally, financing efforts should focus on reducing the risk for private sector players to encourage investment in local manufacturing, which will lead to more affordable vaccines and greater resilience against future health crises [19].

While the development of localized vaccine manufacturing in LMICs is crucial for improving global health outcomes, significant challenges remain. Overcoming these barriers requires a multi-faceted approach, including investments in education and workforce development, strengthening regulatory systems, ensuring predictable market demand, and securing sustainable financing. Only by addressing these interconnected challenges can LMICs develop the capacity to produce vaccines locally, enhance their pandemic preparedness, and reduce their dependence on high-income countries for essential healthcare supplies.

Vaccine inequity has several far-reaching consequences

- Prolonged pandemics: when large populations remain unvaccinated, the virus continues to spread and mutate, undermining global health gains [20]
- Economic impacts: global economic recovery is tied to health security. The International Monetary Fund (IMF) estimated that vaccine inequity could cost the global economy over US$ 9 trillion [21]
- Erosion of trust: Inequitable access can lead to distrust in international institutions and fuel vaccine hesitancy within underserved communities [22]

The case for distributed manufacturing

To address the root causes of vaccine inequity, distributed vaccine manufacturing, producing vaccines in multiple regional hubs rather than a few centralized facilities, has emerged as a crucial strategy. This approach ensures timely access, reduces reliance on international supply chains, and builds local resilience.

Key benefits of distributed manufacturing include:

- Reduced logistical bottlenecks: local and regional facilities help avoid delays caused by export bans, border closures, or shipping disruptions [23]
- Capacity building: establishing manufacturing in LMICs strengthens local scientific expertise, infrastructure, and self-reliance [24]
- Greater responsiveness: in future health emergencies, this model enables faster development, production, and distribution of vaccines tailored to regional needs [25]

Notable initiatives are already underway. The WHO's mRNA vaccine technology transfer hub in South Africa is a landmark effort aimed at transferring the skills, technology, and intellectual property needed for mRNA vaccine production in LMICs [26]. Similar initiatives can help empower countries to produce vaccines for COVID-19, influenza, HIV, and other emerging diseases.

Global vaccine equity is not just a moral imperative; it is a public health and economic necessity. The COVID-19 pandemic has shown that health security cannot be achieved in isolation. Economic and health system disparities between high-income countries and LMICs have contributed to delays in vaccine access, prolonged the pandemic, and damaged trust in global cooperation. By investing in distributed vaccine manufacturing, the international community can reduce dependency, promote health sovereignty in LMICs, and create a more resilient, equitable global health landscape.

Lessons from COVID-19: centralized production bottlenecks, export bans, and the vulnerability of LMICs

The COVID-19 pandemic exposed major weaknesses in global supply chains, disproportionately affecting low- and middle-income countries (LMICs). Key lessons emerged around the risks of centralized production, the consequences of export bans, and the structural vulnerabilities of LMICs in accessing critical health supplies [2].

Building resilience through decentralization and equity

The pandemic underscores the urgent need to decentralize production and strengthen local manufacturing in LMICs. Investing in regional vaccine and medicine

TABLE 1

Vaccine manufacturing progress: comparative analysis

Region	Leading countries	Key manufacturers/ institutes	Key developments	Key challenges	References
Asia	India, Bangladesh, Indonesia	Serum Institute, Bharat Biotech, Biological E, Incepta, SQUARE Pharma, Bio Farma	India is a major global supplier; Bangladesh and Indonesia are expanding domestic and regional vaccine roles	Technological gaps in mRNA production, cold chain logistics issues, and regulatory delays persist	[26,29–32]
Africa	Senegal, South Africa, Egypt, Rwanda	Institute Pasteur de Dakar, Biovac, Afrigen Biologics, VACSERA, BioNTech (Rwanda)	Rwanda hosts BioNTech's mRNA BioNTainer facility (2023); Senegal is advancing the MADIBA project; Egypt is expanding VACSERA's capabilities	Infrastructure and skilled labor shortages, tech transfer hurdles, and regulatory complexities remain key challenges	[33–36]
Americas	Bolivia, Haiti	AGEMED (Bolivia, planned); none in Haiti	Bolivia is planning domestic capacity; Haiti relies on COVAX and NGOs for supply	The region faces infrastructure deficits, no local production, and complete reliance on imports	[37–39]

production can reduce dependency and increase resilience. Additionally, reforms to global institutions, such as the World Trade Organization are needed to regulate export bans during health emergencies and uphold equitable access to essential goods. While initiatives like COVAX aimed to bridge these gaps, they fell short due to inadequate funding and vaccine nationalism. A stronger commitment to multilateral cooperation and equitable distribution mechanisms is essential for future preparedness [27,28].

LOCALIZED VACCINE MANUFACTURING IN LMICS

A critical step in the supply chain

The drive to localize vaccine manufacturing in LMICs has yielded notable progress, particularly in Asia. However, deep regional disparities persist. Africa and Latin America face more severe constraints, with limited domestic production and high dependence on imports (Table 1). Closing these gaps will require sustained investment in biotechnological infrastructure, workforce training, regulatory harmonization, and equitable access to technology. Public-private partnerships and global collaborations such as those seen in South Africa and Senegal, can serve as models to accelerate vaccine independence. A more equitable and resilient global vaccine ecosystem hinges on empowering LMICs to manufacture vaccines not just for their own populations, but for the world.

Asia: examples of active manufacturing of vaccines

These include the production of active pharmaceutical ingredients (APIs), formulation, fill-finish, quality control, and regulatory oversight. Such countries often have WHO-prequalified facilities and established regulatory systems, enabling them to supply vaccines both domestically and internationally. For example, India, Bangladesh and Indonesia, have played important roles in the global vaccine supply chain. India is home to major manufacturers like the Serum Institute of India, which produce and export large volumes of vaccines. Bangladesh also contributes

through Incepta Vaccine Ltd, which are expanding their production and export capacity. Indonesia, well known for the manufacturing capabilities of PT Biofarma. For instance:

- **Serum Institute of India (SII)**: the world's largest vaccine manufacturer by volume, SII produces key vaccines such as those for polio, diphtheria-tetanus-pertussis (DTP), measles, and COVID-19 (COVISHIELD, developed with AstraZeneca) [40]

- **Bharat Biotech**: developed India's first indigenous COVID-19 vaccine, Covaxin®, and is a leader in rotavirus and rabies vaccines [41]

- **Biological E Ltd**: partnered with CEPI (Coalition for Epidemic Preparedness Innovations) and PATH (Program for Appropriate Technology in Health) to manufacture affordable vaccines, including a protein subunit COVID-19 vaccine (Corbevax) [42]

India's vaccine manufacturing capacity has been essential to global health, especially through the COVAX initiative. Yet, it faces persistent challenges: cold chain logistics, regulatory constraints, and limited capacity for next-generation vaccines like mRNA formulations [5].

In Bangladesh, companies such as Incepta Vaccine Ltd and SQUARE Pharmaceuticals have emerged as significant contributors to regional supply, manufacturing vaccines for influenza, tetanus, and hepatitis B [43,44]. Incepta also plans to expand its fill-finish and bulk manufacturing capabilities [43].

Indonesia's Bio Farma is another key regional player, producing a broad portfolio of vaccines and collaborating with international partners to co-develop and scale vaccine innovation. The company has partnered with organizations like the Coalition for Epidemic Preparedness Innovations (CEPI) and MSD (Merck & Co.) to boost vaccine development and local manufacturing [45,46].

Africa: emerging capabilities amid structural constraints

In Africa, vaccine manufacturing remains at an early stage, with over 90% of vaccines still imported, however several countries across the continent are pursuing targeted initiatives to strengthen local production and reduce reliance on external suppliers [47,48]. For instance:

- **Senegal**: the Institut Pasteur de Dakar has a long-standing history of vaccine production, especially for yellow fever. The Manufacturing in Africa for Disease Immunization and Building Autonomy (MADIBA) project, supported by the European Union and CEPI, is building Africa's first regional manufacturing hub for mRNA vaccines [26]

- **South Africa**: the Biovac Institute, a public–private partnership, has collaborated with Pfizer and Moderna for fill-and-finish capabilities of COVID-19 mRNA vaccines. Additionally, Afrigen Biologics—the lead institution in WHO's mRNA technology transfer program—is working to develop an African-owned mRNA vaccine for COVID-19, with plans to expand to tuberculosis and HIV [26]

- **Egypt**: the state-owned VACSERA has scaled up production of Sinovac and AstraZeneca vaccines under local licenses. Egypt aims to expand its portfolio and become a manufacturing hub for Africa and the Middle East [49]

- **Rwanda**: a landmark development took place in December 2023, when BioNTech inaugurated its first

BioNTainer mRNA vaccine production facility in Kigali. These modular manufacturing units are designed to produce up to fifty million doses annually. The facility will manufacture vaccines targeting malaria, tuberculosis, and HIV and is expected to become operational in 2025. This is part of BioNTech's commitment to decentralizing vaccine production and building capacity in LMICs. The project received a €40 million investment from the European Union through the Global Gateway Africa-Europe Investment Package [50–52]

The Americas: still largely dependent on imports

Vaccine manufacturing in the Americas is uneven. While upper-middle-income countries like Brazil and Mexico have existing capabilities, lower-income countries such as Haiti and Bolivia face significant barriers:

- **Haiti** lacks local production entirely and depends on donor support from COVAX and organizations like GHESKIO and Partners In Health for vaccine access and distribution [53–55]

- **Bolivia** has announced initiatives to develop domestic manufacturing, including through AGEMED (Agencia Estatal de Medicamentos y Tecnologías en Salud), but lacks operational facilities or export capacity as of 2024. The region requires substantial international support to overcome foundational deficits in biomanufacturing and regulatory oversight [56,57]

WHAT NUMBER, SIZE, AND TYPE OF FACILITIES ARE SUSTAINABLE?

Achieving sustainable vaccine manufacturing in LMICs requires strategic planning across three core dimensions: the number of facilities, their size and capacity, and the type of technologies employed. Each of these factors influences a country or region's ability to meet disease control targets, maintain resilience in crisis, and ensure long-term economic viability [5,48].

Number: regional versus national hubs

The optimal number of facilities in LMICs depends on population needs, disease burden, and integration within regional supply chains. Rather than every country building its own end-to-end production capacity, an approach that can be economically inefficient and technologically redundant, a more sustainable model prioritizes regional hubs with satellite fill-finish or distribution nodes.

- WHO's 2030 goal for expanding manufacturing capacity in LMICs suggests a minimum of 15–20 regional vaccine production hubs across Africa, Asia, and Latin America to cover basic immunization needs and prepare for pandemics [48]

- Africa CDC's ambition is to produce 60% of the continent's vaccines by 2040. This would require at least 5–7 strategically located full-cycle manufacturing facilities, supplemented by multiple fill-finish plants to ensure regional distribution [58]

In this model, Rwanda's BioNTech plant [50], Senegal's MADIBA project [35], and South Africa's Biovac/Afrigen [59] hubs serve as early examples of regional manufacturing anchors.

Size: balancing economies of scale versus resilience

Large-scale centralized plants, like India's Serum Institute, offer significant economies of scale, driving down per dose costs and enabling mass export. However, such

TABLE 2

LMIC facilities categorisation.

Type	Description	Pros	Cons	References
Fill-finish only	Importing bulk vaccine materials and packaging locally	Faster setup, lower cost, useful for emergencies	Dependent on bulk imports; limited independence	[65,66]
End-to-end traditional	Local production of antigens, formulation, quality control, packaging	Greater autonomy; can target endemic diseases	Higher cost, longer timelines, complex regulation	[61,67]
mRNA/next-gen platforms	Production of nucleic acid vaccines with modular bioreactors (e.g., BioNTainers)	Rapid scale-up, flexible disease targeting	High-tech demand, IP barriers, new regulatory pathways	[68,69]

facilities are less agile during regional disruptions (e.g., export bans, raw material shortages) [60–62].

By contrast, smaller, decentralized facilities may lack scale efficiency but offer greater resilience, especially during pandemics or geopolitical disruptions. They can [23,63]:

- Serve localized outbreaks faster
- Be customized for regional disease profiles (e.g., Lassa fever, dengue)
- Avoid overdependence on one or two mega-producers

A hybrid approach with large regional hubs supported by modular or mid-sized satellite units, offers the best balance for LMICs. The goal is 'right-sized infrastructure': scalable, affordable, and integrated with public health systems [23,64].

Type: fill-finish versus full end-to-end manufacturing

LMIC facilities can be categorized into three types (Table 2):

In this context, Rwanda's BioNTech BioNTainer facility represents a breakthrough in modular mRNA vaccine production [50,52,68]:

- BioNTainers are fully contained, scalable manufacturing units that can be assembled in under 6 months
- Rwanda's facility is designed to produce up to 50 million doses annually and may serve as a template for rapid deployment in other regions
- The project emphasizes technology transfer, local workforce training, and long-term sustainability

Similarly, Afrigen Biologics in South Africa, as part of WHO's mRNA tech-transfer hub, is another example of how platform-based, modular production can diversify regional vaccine options beyond COVID-19 to include HIV, TB, and malaria [26].

The role of modular, scalable manufacturing technologies

Emerging technologies like modular biomanufacturing, exemplified by BioNTech's BioNTainer, are transforming how LMICs can enter and scale in vaccine production [68,70]:

- Benefits [71–73]:
  - Rapid deployment in underserved regions

- Flexible platform for multiple pathogens
- Lower capital investment than traditional factories
- Enhanced standardization and quality assurance

- Limitations [74,75]:
  - Initial dependence on proprietary technologies and partners
  - Regulatory harmonization is still evolving
  - Requires skilled workforce and digital monitoring capabilities

As of 2024, modular production is becoming the preferred model for sustainable, scalable manufacturing in LMICs, especially in regions with fragile infrastructure but high demand for epidemic and endemic disease response.

A sustainable vaccine manufacturing strategy in LMICs must align with regional public health goals, economic efficiency, and technological viability. Instead of duplicating full production capabilities in every country, a network of regional hubs supported by modular facilities and local fill-finish units represents the most pragmatic model [25]. Rwanda's BioNTainer, Senegal's MADIBA, and India's legacy model illustrate different successful approaches adapted to local needs and global supply demands.

SUPPORTING LMIC VACCINE MANUFACTURING

To accelerate vaccine manufacturing capabilities in low- and middle-income countries (LMICs), targeted short-term policy interventions are essential. These measures can catalyze local production while addressing structural barriers. One such intervention is the use of advance market commitments (AMCs), which reduce investment risk for manufacturers by guaranteeing demand. For instance, Gavi's AMC for pneumococcal vaccines successfully incentivized supply at lower prices for LMICs [76]. Similarly, regional pooled procurement mechanisms, like the Pan American Health Organization (PAHO) Revolving Fund, have proven effective in negotiating better pricing and ensuring equitable distribution [77].

Technology transfer initiatives also play a pivotal role. The World Health Organization's mRNA technology transfer hub in South Africa is a key example, enabling LMICs to build capacity for producing next-generation vaccines. These hubs support knowledge sharing and help overcome intellectual property and technical barriers that often hinder vaccine production in lower-income settings [26].

Streamlining regulatory processes is another critical area. Regulatory harmonization and fast-tracking mechanisms, such as those spearheaded by the African Medicines Agency (AMA), which became operational in 2021, aim to unify standards across the continent. This reduces duplication and facilitates quicker approvals for medical products, thereby expediting vaccine availability [78].

Lastly, financial tools such as initial subsidies, tax incentives, and blended finance can significantly de-risk early-stage investments in vaccine manufacturing. Measures like time-bound subsidies and tax relief for vaccine-related research and development are essential. Blended finance models that combine public and private capital, as demonstrated by the Coalition for Epidemic Preparedness Innovations (CEPI) and the International Finance Corporation (IFC), have shown strong potential to engage the private sector in health manufacturing efforts [79,80].

However, building vaccine manufacturing capacity in LMICs cannot be a one-way

transfer of technology and resources. High-income countries, while providing much-needed support, must also ensure that their assistance does not create dependency. Sustainable vaccine manufacturing in LMICs requires coordinated efforts from national governments, regional bodies, global health organizations (e.g., WHO, Gavi, CEPI), donor agencies, private manufacturers, academic institutions, and civil society. These actors collectively enable local capacity, reduce dependency on external suppliers, and support long-term health security and equity. Bilateral development agencies have a critical role to play in fostering this autonomy. Through investments in infrastructure, training, and local innovation, high-income countries can help build self-sufficient systems without creating a dependence on external aid. For example, the European Union's support for Africa's vaccine manufacturing initiative, which focuses on increasing local manufacturing capacity, emphasizes long-term sustainability and self-reliance [81]. This shift from aid to partnership is essential for ensuring that LMICs can produce vaccines independently and sustainably.

RECOMMENDATIONS AND STRATEGIC ROADMAP

To enhance vaccine manufacturing capabilities in low- and middle-income countries (LMICs), a strategic, phased approach is crucial, involving coordinated action across local, regional, and global stakeholders. Immediate actions must focus on strengthening foundational infrastructure, technology transfer, and regulatory frameworks, while long-term goals should concentrate on scaling production, fostering innovation, and ensuring sustainability [2].

Immediate priorities (0–5 years)

At the local level, governments must invest in building robust regulatory environments, strengthening public health institutions, and incentivizing domestic vaccine manufacturing through financial support and tax relief. Partnerships with multinational pharmaceutical companies for technology transfer and knowledge-sharing are essential for rapid capacity building [26]. Regionally, collaborative frameworks like the African Union's Partnerships for African Vaccine Manufacturing (PAVM) should be expanded, facilitating pooled procurement and shared resources. On the global stage, multilateral organizations such as Gavi and CEPI must continue their support for R&D and infrastructure development, with an emphasis on equitable access and resource sharing [82].

Mid-term actions (5–10 years)

In the next 5–10 years, the focus should shift to scaling up production, developing domestic supply chains, and fostering local innovation. LMICs should work toward achieving greater self-reliance in vaccine manufacturing, reducing dependency on external sources. Regional networks should be strengthened, facilitating better coordination and standardization across countries to ensure equitable distribution during global health emergencies. At the global level, governance structures must be established or refined to ensure the fair distribution of resources and vaccines, addressing issues of intellectual property flexibility, and ensuring that vaccines are produced where they are most needed [83].

FINAL REMARKS

Building long-term vaccine manufacturing capacity in low- and middle-income countries (LMICs) is not just a technical necessity but a critical investment in resilience, sovereignty, and equity. The COVID-19 pandemic revealed the vulnerabilities of a global health system heavily reliant on

external vaccine suppliers, leaving LMICs exposed to supply chain disruptions and limited access to life-saving vaccines. By establishing robust local manufacturing capacities, LMICs can secure their own health futures, reduce dependence on foreign vaccine producers, and be better prepared for future pandemics. Vaccine sovereignty enables nations to prioritize the health needs of their populations, respond rapidly in emergencies, and address the specific disease burdens they face.

However, local vaccine manufacturing is not simply a technical challenge; it is a deeply political and economic project. Achieving this goal requires strong political will, targeted investment in infrastructure, and the development of sustainable regulatory frameworks. It also necessitates the creation of strategic partnerships between governments, international organizations, and the private sector to ensure that knowledge, resources, and technologies are effectively transferred and adapted to local contexts.

Ultimately, sustained collaboration and investment are essential to achieving long-term success. This is a shared global responsibility that demands action from all stakeholders, including national governments, multilateral organizations, and the private sector. It is crucial that efforts are coordinated and sustained over time to create an ecosystem that fosters innovation, promotes equity, and guarantees access to vaccines for all. By taking bold, decisive steps now, we can empower LMICs to lead in vaccine manufacturing, ensuring a more equitable, resilient, and sustainable global health system for generations to come.

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AUTHORSHIP & CONFLICT OF INTEREST

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