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REVIEWS



# Capacity Building for Vaccine Manufacturing Across Developing Countries: The Way Forward

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## ABSTRACT

Approved vaccines prevent 2 to 3 million deaths per year. There is a lack of equitable access to vaccines in the low- and middle-income developing nations. Challenges in the life cycle of vaccine production include process development, lead time, intellectual property, and local vaccine production. A robust and stable manufacturing process and constant raw material supplies over decades is critical. In a continuously evolving vaccine landscape, the need of the hour for developing nations is to manufacture their own vaccines besides having supply security, control over production scheduling and sustainability, control of costs, socio-economic development, and rapid response to local epidemics. There is a need for capacity building of workforce development, technology transfer, and financial support. Technology transfer has improved vaccine access and reduced prices of vaccines. Capacity building for the manufacturing of vaccines in developing countries has always been an area of paramount importance and more so in a pandemic situation.

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## 1. Introduction

Prevention of diseases by vaccination is one of the most significant achievements in medical research history.<sup>1</sup> It has become a key to the cost-effective reduction of mortality, improvement of life expectancy, and economic growth. As per the World Health Organization (WHO), approved vaccines prevent 2 to 3 million deaths per year.<sup>2,3</sup> These numbers are projected to increase by at least 6 million if all children are vaccinated as per the recommended vaccination schedule. At present, 19.5 million infants worldwide are still at risk of vaccine-preventable diseases (VPDs) because they miss out on basic vaccines.<sup>4</sup> The primary reason behind this is the lack of equitable access to basic vaccines in the low-income and middle-income developing nations. These nations are largely dependent on imports. Some countries with relatively high per capita income are not eligible for support from Gavi, the Vaccine Alliance (GAVI) in accessing new vaccines.<sup>5</sup> In 2008, the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property was adopted at the World Health Assembly.<sup>6</sup> In 2010, nearly 200 countries committed to a shared global health vision called the “Decade of Vaccine Initiative (DoV) (2010–2020).” The main aim was to achieve 90% vaccination coverage in developing countries to prevent around 7.6 million under-5 child mortality. The vaccine industry in all countries was supposed to play a significant role in these initiatives.<sup>7</sup> Fortunately, during the “Decade of Vaccines,” 20 million additional children, and at least 90% coverage of the three-dose diphtheria-tetanus-pertussis vaccines in more than hundred countries were vaccinated.<sup>8</sup> This initiative also contributed to increased recognition of the socio-

economic benefits of immunization beyond reducing the VPDs burden and increased demand for data and analytical methods to quantify the economic impact and support decision-making.<sup>8</sup> Return on investment (ROI) and investment cases have been actively used by global health stakeholders to link specific health investments’ implications and costs.<sup>8</sup> Sim *et al.*,<sup>8</sup> estimated economic impact by using cost-of-illness and value-of-a-statistical-life models. They used this estimation with immunization program costs and derived the ROI from immunization programs against 10 pathogens for 94 low- and middle-income countries (LMICs) between 2011 and 2030. Using the cost-of-illness approach, ROI for one dollar invested in immunization against the 10 selected pathogens was 26.1 USD from 2011 to 2020 and 19.8 USD from 2021 to 2030. Using the value-of-a-statistical life approach, return on investment was 51.0 USD from 2011 to 2020 and 52.2 USD from 2021 to 2030. The results showed continued high ROI from the immunization programs. The ROI estimates can help country policy makers and decision makers in mobilizing resources for immunization.<sup>8</sup>

The ongoing coronavirus disease (COVID-19) pandemic is a timely reminder of the tenuous nature of the world’s vaccine supply and the lack of widespread vaccine manufacturing expertise. The annual reports of United Nations Children’s Fund (UNICEF) over the years (2015–2019) have shown that out of the majority of the goods that were procured from different countries are either vaccines or biologicals (Figure 1).<sup>9–13</sup> GAVI started with six vaccines from five suppliers in five countries. Till date, 430 new vaccine introductions were launched by them. The current portfolio targets 18

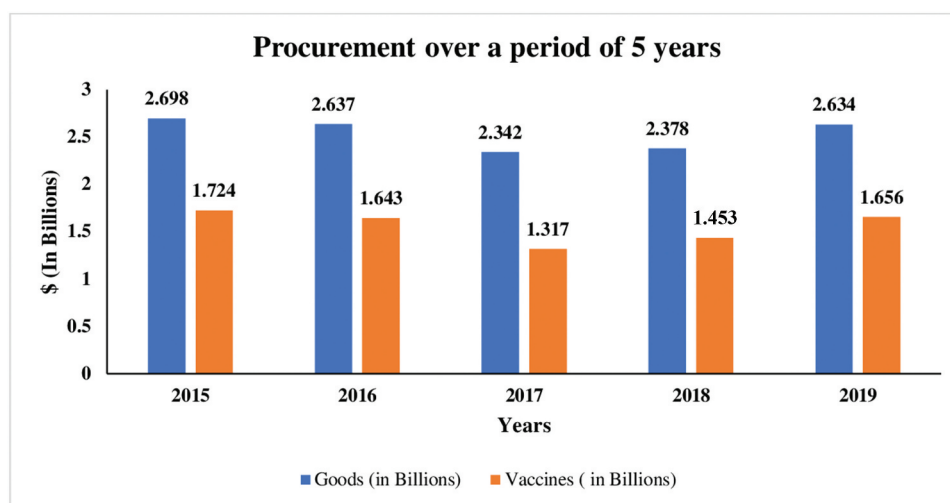


Figure 1. Contribution of vaccines among the goods procured by UNICEF over the years (2015–19).<sup>9–13</sup>

diseases, involving 17 suppliers in 11 countries, impacting affordability and supply security. The number of manufacturers from Developing Countries Vaccine Manufacturers' Network (DCVMN) contributing to GAVI markets increased from 4 to 10 between 2012 and 2018. Moreover, 55% of the total doses were supplied by DCVMN to GAVI between 2012 and 2018 (Figure 2).<sup>14</sup> Even during the COVID-19 pandemic, there are only a few countries with exceptions who are actually actively involved in vaccine development and manufacturing. This also has brought a new emphasis to the local production of vaccines. Local production will require interested countries to work on technology transfer/assimilation, innovation, and capacity-building. Capacity-building interventions, in particular, can take a variety of forms that include technical support, in-depth consultations, web-based and in-person training sessions, online learning options, guidance materials in the form of knowledge products, and skills-based courses among others such as coaching and mentoring.<sup>15</sup>

In this review, we are going to highlight the present challenges to start local vaccine manufacturing in general with particular emphasis on the developing countries and the role of capacity building as a possible solution to counter these

challenges and thereby not only increase the vaccine coverages in their respective countries but also export them to other nations.

## 2. Challenges involved in vaccine manufacturing

### 2.1. Challenges in life cycle of vaccine manufacturing

As highlighted by Plotkin *et al.*, there are several challenges involved in the entire life cycle of vaccine production. Challenges include production facilities, equipment, life cycle management, intellectual property (IP), product portfolio management and process development, process maintenance, and lead time. A robust and stable manufacturing process and constant raw material supplies over decades is critical to ensure long vaccine life cycle in a market.<sup>16</sup>

### 2.2. Challenges to start a new vaccine manufacturing facility

There are a significant number of barriers to starting a vaccine production facility. Some of them are listed below:<sup>17</sup>

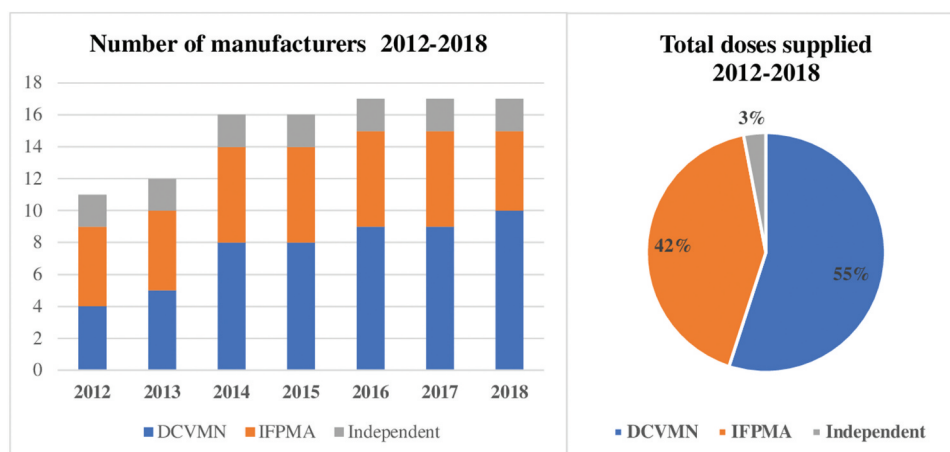


Figure 2. Developing country vaccine manufacturers' contribution to GAVI markets from 2012 to 2018 (Adapted from Pagliusi *et al.*, 2020).<sup>14</sup>

### 2.2.1. Investment

There is a requirement of a significant capital, of an order of tens or hundreds of millions of dollars, to start a commercial vaccine production facility. Moreover, it requires significant fixed and ongoing maintenance costs. Any new change in technology that impacts how vaccines are packaged and delivered may disrupt the vaccine industry by further market segmentation with different product presentations of the same vaccine. For example, a change in the primary containers. In addition to the costs of new technology development, any decrease or alteration in the product life cycle of the original vaccine, full costs of the original presentation are not recovered, and the manufacturer is forced to invest further to maintain market share. Facilities can cost 50–500 million USD per antigen based on the high complexity of design, automation, segregation, utilities, contamination controls, and as much as 700 million USD for multiple vaccines. Current good manufacturing practices (cGMP) space may cost 600 USD/ft<sup>2</sup>; non-cGMP space may cost 350 USD/ft<sup>2</sup>; clean rooms and containment rooms may cost more.<sup>16,17</sup>

### 2.2.2. Operating costs

There are relatively high operating costs involved in acquiring occasionally, some specific raw materials, skilled personnel, and also running utilities for vaccine production. Even if there is no product manufacturing, many of these costs are incurred. Majority of the operating costs are attributed to fixed cost, which is a function of the facility design.<sup>17</sup>

Generally, some equipment across platforms (bioreactors, filtration, and chromatography equipment, filling, and lyophilization equipment) are common, but the sequence of operations and the specific cycles for each product vary. Each product or family of products demands a dedicated facility and production team. This allows flexibility to address unpredictable demand but adds to the operating costs. Labor costs vary significantly by country, depending on the availability of local expertise. Mostly labors include both locals and expatriates. Most expatriate staff require higher total compensation and benefits than local employees, increasing the overall labor costs. Vaccine production mainly needs biological raw materials (e.g., yeast extract, natural or recombinant enzymes), adding inherent biological variability to the manufacturing or analytical processes. These raw materials are specialized in nature and may be limited in supply and subject to shortages. Moreover, materials of animal origin carry the risk of adventitious agents that may contaminate the production process. Raw materials of animal origin are subject to extensive testing for viral or other microbial contamination and are generally sourced from regions free of certain diseases. Due to the short supply, the prices are on the higher side and interrupts production leading to vaccine shortages. Even having multiple suppliers for critical materials to manage short supply, the order volumes from each supplier gets reduced, resulting in higher prices. However, with local production of vaccines, the prices are estimated to be as low as 15% of those in high-resource countries because of cost savings in consumables.<sup>16</sup>

### 2.2.3. Long durations to establish production facility

It takes years to establish a fully integrated commercial vaccine production facility. During this time, unless there is an independent functional business, there is usually no or very limited income until both product registration and commercialization are complete. There are numerous extra costs (10–100 million USD) and factors causing 5–10 years or even more timeline extensions. Secondly, several key factors need alignment to deliver a successful project, viz. a suitable market niche and purchaser, a suitable technology transfer partner, hiring skilled workers, consultants, and specialized firms, and building GMP compliant facilities as well as coordinating all aspects of the project.

When considering the commercial viability of vaccine manufacturing, key considerations include:

- Facility type and scope that has a significant bearing on the time to reach commercial output and the number of years of investment before moving into a positive cash flow situation.
- Production demand forecast has a major impact on the ongoing cost of manufacturing once the facility is fully operational. It can alone impact the ability to repay initial investment costs relating to facility design and construction since the initial level of profitability is a key determinant of the rate at which upfront facility design and construction costs can be repaid.

Both the above points need to be explored and integrated together to determine a project's financial feasibility. A rigorous Front-End Loading (FEL) phase can decrease project costs by an average of up to 20%, irrespective of the project size. As the FEL phase progresses and the market demand and project scope becomes better defined, it is crucial to continuously verify that the business case remains financially viable. A large percentage of projects often do not make it through the full FEL phase due to a lack of financial viability (Table 1).<sup>17</sup>

### 2.2.4. Industrial cluster

The lack of specific expertise and resources in the region makes it hard to get supplies, skilled workers and technical support. "Industry cluster" is defined as the concentration of interrelated individuals, organizations and institutions in different geographical locations which compete and collaborate through knowledge accumulation and intellectual capital. One such example of an industry cluster is India's biotechnology industry wherein the western cluster has 137 biotech companies, the southern cluster has 172 companies and the northern cluster, also known as the National Capital Region (NCR) is best known for its research institutes and government bodies.

**Table 1.** Estimated cost and timelines for fully integrated and form fill vaccine facility type.<sup>17</sup>

Facility/Volume	Low (10 million dose/year)	High (30 million dose/year)
Fully integrated	Cost: ~\$30-65 million Time: 3.5 to 7 years	Cost: ~\$105-225 million Time: 7 to 10 years
Form-fill Only	Cost: ~\$14-29 million Time: 2.5 to 5 years	Cost: ~\$46-98 million Time: 5 to 7 years

India, with its large, skilled english-speaking workforce and affordable R&D, is becoming an increasingly attractive target for establishing operations and alliances. For example, in 2009, Switzerland-based Lonza announced plans to set up an R&D and manufacturing plant in India that will serve as the company's manufacturing base, while in 2010, US-based Biogen-Idec announced that it would be launching its entire drug portfolio in India.<sup>17,18</sup>

- **Industrial Policy:** Policy intervention through industry-specific policies plays a vital role. Any intervention or government policy that augments the business environment or changes the structure of economic activity toward sectors, technologies, or tasks are expected to offer better prospects for economic growth or societal welfare than would occur in the absence of such intervention. The United Nations Industrial Development Organization (UNIDO) is a specialized agency of the United Nations that promotes industrial development for poverty reduction, inclusive globalization and environmental sustainability.<sup>19</sup>

### 2.2.5. Pricing and competition

There is severe global pressure to continuously lower vaccine pricing. Many older and larger firms have already paid off their facilities and can sell some portion of their production volume near or at the cost of goods. The private and developed world markets that offer the most profit, face intense competition from established, and well-reputed companies. The new vaccine pricing process is quite complicated and has long-standing scientific, medical, and public health consequences. Pricing has a significant impact on new vaccine adoption and, thereby, culminate or thwart years of research and development and public health efforts. Typically, pricing strategy consists of the following eleven components: (1) Conduct a target population analysis; (2) Map potential competitors and alternatives; (3) Construct a vaccine target product profile (TPP) and compare it to the projected or actual TPPs of competing vaccines; (4) Quantify the incremental value of the new vaccine's characteristics; (5) Determine vaccine positioning in the marketplace; (6) Estimate the vaccine price-demand curve; (7) Calculate vaccine costs (including those of manufacturing, distribution, and research and development); (8) Account for various legal, regulatory, third-party payer and competitor factors; (9) Consider the overall product portfolio; (10) Set pricing objectives; (11) Select pricing and pricing structure. Since its introduction to the US Market in 2003, an example of FluMist highlights the importance of initial vaccine pricing and how a high price can impede a new vaccine's use and success. There was optimism and anticipation for the approval of FluMist, a live attenuated influenza virus intranasal vaccine, less painful and more convenient alternative to standard intramuscular influenza vaccine, especially among children. Focusing on these advantages and buoyed by initial year sales projections of 4 to 6 million doses, MedImmune and Wyeth sunk \$50 million in marketing and advertising and established a \$40 to \$70 per dose price, over four times that of the

intramuscular vaccine. However, first-year sales fell far (over 75%) short of initial projections, as major insurers and purchasers balked at covering and carrying the high-priced vaccine when a viable and much less expensive inactivated influenza vaccine was present. While FluMist's relatively high price was not the only reason behind its poor adoption (e.g., skepticism remained about the live virus' safety and the 5 to 49-year-old approved population), it certainly played an important role. This financial debacle left MedImmune with large inventories of unused vaccines and led to the dissolution of the partnership between MedImmune and Wyeth in April 2004. Chastened, MedImmune slashed FluMist's price to \$23.50 per dose the following influenza season where its price has since hovered.<sup>17,20</sup>

### 2.2.6. Limited partnership opportunities

Vaccine production is difficult and many companies will be reluctant to invest resources to transfer their knowledge or supply product to a new and unproven company who could be a future competitor. The critical elements are the importance of technology transfer and the tech transfer receiving sites i.e., the facilities in these countries that produce vaccines locally, having specialized equipment and personnel. National regulatory authorities (NRAs) in manufacturing have an important role in assuring safety, efficacy, and product quality in LMICs. As per WHO, only 30% of NRAs among its member states can regulate medical products effectively in their countries. Expanding vaccine manufacturing without adequate regulatory capacity in those countries can lead to poor product quality, adverse effects and could seriously undermine public trust.<sup>17,21</sup> All these factors may become a potential hindrance for partnerships between companies for vaccine manufacturing.

### 2.2.7. Hiring and training personnel

Specialist expertise are needed in setting a new vaccine manufacturing facility. Hiring foreign experts to work in key facility positions is often necessary. Local skilled workers will require significant training which may include being sent abroad for months at a time. Companies around the world tend to underestimate the time and cost of finding and training their local and expat workforce.<sup>17</sup>

The appropriate efforts to recruit, train, and retain a skilled local workforce are essential to support long-term sustainability and viability of developing country vaccine manufacturers.<sup>22</sup>

A variety of financial incentives (good financial remuneration, performance based monetary incentives, and rewarding upon returning to home country) and non-financial incentives (supportive work atmosphere, cordial employer-employee relationship, development opportunities through training, promotion and recognition, and innovation opportunities) should be included in comprehensive brain drain management strategies.<sup>23</sup>

The Institute of Biotechnology in Hyderabad, India has, with participation of faculty from Bharat Biotech Ltd, a DCVMN, developed a curriculum for a 2 months practical



training course in industrial biotechnology for frontline supervisors of Biotech and DCVMN staff. In August 2012, the first edition of this course was successfully delivered.<sup>22</sup>

### 2.2.8. Changes to the landscape over time

Given the lengthy development process, there is a risk that a well-documented need at the time of starting a project may no longer be a need by the time the vaccine is approved, resulting in a smaller or absent market. Therefore, developers should assess the projected needs on a continuous basis. Sometimes decision to localize some portion of vaccine production is taken based on the agreement of a government to buy a huge quantity of vaccines at a relatively high price, exclusively from a local manufacturer and their technology transfer partner. A new local facility can take long duration. In the meantime, the government may change its decision of exclusivity of the purchasing program or change the buying price due to various reasons, like a change of power, budget cuts, or the arrival of cheaper competition in the open market.<sup>17</sup>

## 3. Vaccine manufacturing landscape in developing countries

The vaccine manufacturing landscape in developing countries is evolving continuously. The need of the hour for developing nations is to manufacture their own vaccines besides having supply security, control over production scheduling and sustainability, control of costs, socio-economic development, and rapid response to local epidemics, including emerging infectious diseases.<sup>16</sup> But the critical aspects for the establishment of vaccine production capacity differ from country to country. The challenges in developing countries include the local availability of experts, constant source of raw materials, consumables, equipment, market access, import policy, IP, lack of regulatory framework in GMP inspection, and long timelines for dossier review and approval. Other critical aspects include the construction of facility, financial support, and acquisition of technology.<sup>24,25</sup> However, despite of the bottlenecks, research institutes in these countries, particularly in the more resourceful emerging economies, have an enormous potential to contribute for vaccine research, development, and production. There is need of national and international investments for capacity building, including workforce development, innovation, new technologies, and infrastructure for technological development and production infrastructure.<sup>26</sup>

## 4. Challenges in vaccine production in developing countries

### 4.1. Workforce development in vaccine production

There are very few vaccine manufacturers in developing countries, and hence there is a lack of experienced and skilled people in vaccine production with a few exceptions such as China and India. As mentioned earlier, vaccine manufacturing needs specific experts to start and run any facility. That is why all manufacturers must have a permanent multi-disciplinary workforce program. The training must be hands-on, monitored properly, and evaluated continuously. Moreover, there

are challenges in the form of high cost and long period of the training program, loss of personnel due to salary, search of more rewarding employment opportunities and lack of training opportunities in top manufacturers.<sup>26</sup>

### 4.2. Challenges in technology transfer in developing countries

The term “transfer of technology” is a process by which technology developed for one specific use or sector becomes applicable in a different productive setting. Technology transfer may refer to a process within or across national boundaries, and on a commercial or non-commercial basis. It may also refer to the physical movement of assets or to immaterial elements such as know-how and technical information, or most often to both material and immaterial elements. Technology transfer may be linked to the movement of physical persons or more specifically to the movement of a specific set of capabilities.<sup>27</sup> Technology transfer to developing countries increases the global capacity, ensures access to the vaccines and thereby significantly improves the health of the population.<sup>28</sup> However, there are few challenges in it too.

The main challenges, in order of priority, from a recipient’s perspective are:<sup>28</sup>

- Vaccine manufacturers from over 70% of developing countries face inadequate R&D capacity to support technology transfer;
- Lack of experience in R&D staff;
- Resource prioritization at the company level;
- License negotiation skills and training;
- Evaluation and assessment for quality of technologies.

The main challenges, in order of priority, from the technology provider’s perspective include:

- R&D ability and budget to support technology transfer;
- Business case/sustainability;
- Clinical trial expertise;
- Quality control facility and human resources;
- National drug regulatory authority capacity weakness (reported in some countries).

### 4.3. Regulatory standard challenges

National regulatory authorities (NRAs) are responsible for ensuring that products released for public distribution, including vaccines are evaluated properly and meet international standards of quality and safety.<sup>29</sup>

WHO vaccine prequalification depends on NRAs deemed “functional,” or that have been WHO-listed as operating at a minimum of maturity level 3. Manufacturers can apply for prequalification of a vaccine only if their NRA is “functional” or a WHO-listed Authority operating at maturity level 3 or above.<sup>30</sup> Such NRAs have the following:<sup>30</sup>

- A published set of requirements for licensing;
- Perform surveillance of vaccine field performance;
- Operate a system of lot release;
- Use a national control laboratory;

- Conduct regular inspections of vaccine manufacturing sites for good management practice;
- Evaluate the clinical performance of vaccines manufactured in their country.

Some countries which have received WHO certification for their NRAs include India, Brazil, Indonesia, China, Mexico, Cuba, etc.<sup>31</sup>

## 5. Capacity building for vaccine manufacturing in developing countries

There is a need for capacity building in terms of workforce development, technology transfer, construction of facility, financial support, etc.

### 5.1. Work force development

An adequate and sustainable approach to workforce development in vaccine production will require a broad and complex range of conditions. It will require local capacity for long-term strategic planning, such as multi-year development and production, managerial skills, taking into account the challenges faced by vaccine production. The institutional academic and technological competencies, the regulatory situation, market, IP, capacity to manage risks and raise capital must be considered beyond financial considerations. The international organizations have an important role in enhancing the workforce for vaccine development and manufacturing.<sup>26</sup>

### 5.2. Technology transfer

WHO conducted survey has highlighted that technology transfer to developing countries has contributed significantly in increasing vaccine supply, increased access to many vaccines, and lower prices of vaccines. Establishing local vaccine manufacturing is not always cost-effective. Vaccine manufacturing should be seen from national health security rather than purely as a commodity. The establishment of a country-specific vaccine policy may assist in identifying how and when to consider local production. For technology transfer to be of help to everyone, it must be facilitated by a commitment from the government to support the technology transfer or a large local or regional market.<sup>28</sup>

### 5.3. Build global vaccine manufacturing capacity to respond to pandemics

Sell *et al.*<sup>32</sup> published their research by conducting expert interviews on pandemic preparedness, vaccine design, and vaccine manufacturing. This study was done before the start of the COVID-19 pandemic. Based on the study, they have provided recommendations as follows:

- **To expand the vaccine development paradigm by substantial expansion of research and development in platform technologies, and additional technologies that allows faster development and manufacture of medical countermeasures (MCMs) to respond to a pandemic**

The use of platform technologies with a common mechanism (e.g., common device, delivery vector, or cell line for multiple vaccines) can enable producers to rapidly scale up manufacturing and transfer between different biological MCMs, e.g., vaccines (Table 2 and Table 3). With the use of same production mechanism for delivering a wide range of products, manufacturers may allow regulators to approve products based on platform rather than product characteristic. These new approaches can substantially improve surge production capacity and should become a major focus of pandemic vaccine preparation efforts for the future.

- **Encourage flexible/contract manufacturing to address limitations related to manufacturing specialization**

Flexible manufacturing techniques can help production facilities to switch more rapidly between products, scale-up production, or relocate production capacity. Flexible manufacturing technologies include single-use components for all stages of manufacturing (production, processing, and fill-and-finish), modular factory design, portable modular manufacturing, and continuous processing. Many of these techniques are presently in commercial use while others are in development. The advantage with modular facilities is that they allow manufacturers to customize continuously and to reconfigure equipment and accommodate new products or processes.

- **Increase flexible vaccine production and global access through localized distributed manufacturing**

Approximately, 80% of the vaccines are manufactured by global pharma giants namely GSK, Merck, Novartis, Pfizer and Sanofi Pasteur which are located in the US and Europe. As a result, many regions lack significant vaccine manufacturing capacity. These areas are ones where there is high demand for vaccines as there exist an increased risk of endemic diseases and outbreaks.

Novel technologies such as utilizing DNA/RNA synthesis, 3D printing, mini-labs, and product design would make distributed manufacturing feasible for a broad range of vaccines across the globe. These technologies would not only enable decentralized production but will also provide flexibility to accelerate transition between different product lines. Combined with local testing and quality assurance, a new regulatory approach would be needed as well. Vaccine companies would require sharing of their IP in new ways for their products to be produced in a distributed way. Implemented at mass scale, distributed manufacturing would not only provide value for routine use but also be beneficial during pandemics.

- **Prepare measures to reduce timelines associated with regulatory requirements**

Where feasible from a safety point of view, alternative review strategies by the regulatory authorities such as the Food and Drug Administration (FDA) might speed-up the development, production, and distribution of innovative vaccines. For example, the FDA could consider regulating some

**Table 2.** Major vaccine platforms – Merits and Demerits and examples of licensed vaccines.

Type of vaccine	Merits	Demerits	Examples of licensed vaccines
Live Attenuated	<p>Produces robust cellular and humoral immune response<sup>33</sup></p> <p>Confers lifelong immunity<sup>33,34</sup></p> <p>Intranasal administration provides local mucosal immunity through IgA<sup>34</sup></p> <p>Easy to produce and inexpensive<sup>3,4-36</sup></p> <p>Less adverse effects<sup>36</sup></p>	<p>Safety issues in immunocompromised patients<sup>33</sup></p> <p>Not suitable for all age groups<sup>36</sup></p> <p>Requires Biosafety Level - 3 (BSL-3)<sup>37</sup></p> <p>Requires cold chain<sup>35</sup></p>	<p>Oral Polio Vaccine (OPV), Measles Mumps Rubella (MMR), Bacillus Calmette–Guerin (BCG), Chicken Pox, Yellow Fever, Smallpox, Rotavirus<sup>35</sup></p>
Whole Inactivated	<p>Infectivity destroyed without compromising the immunogenicity<sup>38</sup></p> <p>Safe as the pathogen is dead<sup>33</sup></p> <p>Produces high titer of neutralizing antibodies<sup>36</sup></p> <p>Stable vaccines<sup>38</sup></p> <p>Can be freeze dried and does not require cold chain<sup>35</sup></p> <p>Easy to prepare<sup>36</sup></p>	<p>Requires the use of adjuvants as it produces weak immune response<sup>34</sup></p> <p>Inactivation can affect immunogenicity of the antigen<sup>33</sup></p> <p>Antibody titers reduce over time and require booster doses<sup>33</sup></p> <p>Does not produce cellular immune response<sup>33</sup></p> <p>Requires live virus and facility to grow large amounts<sup>37</sup></p>	<p>Hepatitis A, Rabies, Flu, Inactivated Polio Vaccine (IPV), Japanese encephalitis<sup>33-35,39</sup></p>
Subunit			
(a) Recombinant Subunit	<p>Safety during production<sup>33</sup></p> <p>Can be administered to immunocompromised patients<sup>33</sup></p> <p>Does not require the handling of infectious agents<sup>33</sup></p> <p>Established safety profile and cost-effective production<sup>34,36</sup></p>	<p>Weaker immune response over time<sup>38</sup></p> <p>Lower immunogenicity<sup>33,36</sup></p> <p>Requires several booster doses and adjuvants<sup>33,36</sup></p> <p>Small size of the antigen affects the uptake by Antigen Presenting Cells (APCs)<sup>33</sup></p>	<p>Hepatitis B, Hepatitis C, Acellular pertussis, Influenza<sup>33,34</sup></p>
(b) Polysaccharide	<p>Provides an alternate for vaccines against pathogens with abundance of polysaccharide antigens<sup>33</sup></p> <p>Stimulates B-cell responses resulting in type-specific antibody production that enhances ingestion and killing of the pathogens by phagocytes<sup>40</sup></p> <p>Acceptable safety profile, immunogenic, and effective in older children and adults<sup>41</sup></p> <p>Relative simplicity of production<sup>42</sup></p>	<p>Poorly immunogenic and therefore less effective in children &lt;2 years old<sup>43</sup></p> <p>Responses seldomly enhanced by booster doses<sup>33</sup></p> <p>Only IgM isotype and IgG2 subtype are induced leading to limited antibody mediated effector functions<sup>33</sup></p> <p>Poor memory responses<sup>33</sup></p>	<p>Pneumococcal polysaccharide vaccine (PPSV or PPV-23)<sup>33</sup></p>
(c) Conjugate	<p>Enhances the poor immunologic responses produced by polysaccharide vaccines as it induces T-dependent responses<sup>33</sup></p> <p>Safe, immunogenic in young infants and induces long-term memory<sup>44</sup></p> <p>Generation of mucosal immune response – (secretory IgA and mucosally active IgG)<sup>45</sup></p> <p>Mucosal carriage reduction – a prerequisite of herd protection<sup>45</sup></p>	<p>Absence of cellular responses<sup>33</sup></p> <p>Requires adjuvant and booster doses<sup>33</sup></p>	<p><i>Streptococcus pneumoniae</i>, <i>Neisseria meningitidis</i>, Typhoid, <i>Haemophilus influenzae</i> type b<sup>33</sup></p>

(Continued)



Table 2. (Continued).

Type of vaccine	Merits	Demerits	Examples of licensed vaccines
Virus Like Particles (VLPs)	Scalability of production <sup>33</sup> Noninfectious in nature since it lacks the genetic material <sup>34</sup> Highly immunogenic <sup>46</sup> Stimulates robust cellular and humoral immune responses due to antigenic epitopes <sup>46</sup> Possess excellent adjuvant properties <sup>47</sup> Good safety profile <sup>33,36,48</sup> Long term gene expression <sup>38</sup> Induces robust cellular and humoral response <sup>33,36,48,49</sup>	Assembly of the particles sometimes poses challenges <sup>33</sup> Challenges – optimal quality, stability, and good immunogenicity at high yield <sup>38</sup>	Human Papillomavirus (HPV), Hepatitis B <sup>33</sup>
Viral Vector		Risk of chromosomal integration and oncogenesis <sup>48,49</sup> Pre-existing immunity to vectors <sup>33,48,49</sup> Risk of infection <sup>48</sup> Inflammatory adverse events <sup>48,49</sup> Some vaccine candidates require storage at < –20°C <sup>33</sup>	Ebola <sup>33,39</sup>
Nucleic Acid (a) RNA	Options for multivalent formulations <sup>48,49</sup> High safety – cannot cause disease <sup>35,48</sup> Enhanced antigen expression due to direct delivery to the cytosol <sup>38</sup> Rapid development and production <sup>48</sup> No risk of genetic integration <sup>48</sup> Induces strong humoral and cellular responses <sup>48,49</sup>	Requires cold chain for stability and longevity <sup>49</sup> Weak immunostimulation due to lack of interaction with endosomal RNA receptors <sup>38</sup> Inflammatory/Adverse reactions possibility <sup>48,49</sup> High cost <sup>48</sup> Booster doses required for long lasting and robust immunity <sup>49</sup>	SARS-CoV-2 <sup>50</sup>
(b) DNA	Rapid development and production <sup>48</sup> Safe – cannot cause disease and no risk of infection <sup>35,38,48</sup> Long term stability <sup>48,49</sup> Inexpensive <sup>34,38</sup> Induces both humoral and cellular responses <sup>38,48,49</sup>	No real-world experience till date <sup>49</sup> Requires specialized delivery tools <sup>36,49</sup> Poor immune response <sup>36,48</sup> Repeated doses may cause toxicity <sup>36,48</sup> Risk of genetic integration <sup>48,49</sup>	SARS-CoV-2 <sup>50</sup>

**Table 3.** Characteristics of different expression systems for recombinant protein based vaccines.

Expression Systems	Characteristics	Examples of vaccine candidates approved for human use
Mammalian cells	<ul style="list-style-type: none"> <li>• Lower cost<sup>51</sup></li> <li>• High production time<sup>52,53</sup></li> <li>• Hard propagation<sup>52,53</sup></li> <li>• Medium product yield<sup>53</sup></li> <li>• High product quality<sup>52</sup></li> <li>• Very low scale-up capacity<sup>52,53</sup></li> <li>• Contamination risk is high<sup>52,53</sup></li> <li>• Purification cost is high<sup>52</sup></li> <li>• Humanized glycosylation pattern<sup>52</sup></li> <li>• Good secretion<sup>52</sup></li> <li>• Slow growth rate<sup>52</sup></li> <li>• Pyrogen free<sup>52</sup></li> <li>• Good protein folding<sup>52</sup></li> </ul>	Shingrix® (GSK) Host: CHO Cells Disease: Herpes Zoster <sup>54</sup>
Yeast	<ul style="list-style-type: none"> <li>• Medium overall cost<sup>52,53</sup></li> <li>• Medium production time<sup>52,53</sup></li> <li>• Easy propagation<sup>52,53</sup></li> <li>• High product yield<sup>52,53</sup></li> <li>• Medium product quality<sup>52</sup></li> <li>• High scale-up capacity<sup>52,53</sup></li> <li>• Low contamination risk<sup>52,53</sup></li> <li>• Medium purification cost<sup>52</sup></li> <li>• Good secretion<sup>52</sup></li> <li>• Ease of cultivation<sup>52</sup></li> <li>• Ease of genome modifications<sup>52</sup></li> <li>• Good protein folding<sup>52</sup></li> <li>• Glycosylation<sup>52</sup></li> </ul>	Gardasil-9® (Merck & Co.) Host: <i>S. cerevisiae</i> Disease: HPV <sup>54</sup>  Engerix®-B (GSK) Host: <i>S. cerevisiae</i> Disease: Hepatitis B <sup>54</sup>
Bacteria	<ul style="list-style-type: none"> <li>• Low overall cost<sup>52,53</sup></li> <li>• Low production time<sup>52,53</sup></li> <li>• Easy propagation<sup>52,53</sup></li> <li>• High product yield<sup>53</sup></li> <li>• Low product quality<sup>52</sup></li> <li>• High scale-up capacity<sup>52,53</sup></li> <li>• Medium product yield<sup>52</sup></li> <li>• Medium contamination risk<sup>52,53</sup></li> <li>• High purification cost<sup>52</sup></li> <li>• Poor secretion<sup>52</sup></li> <li>• Ease of cultivation<sup>52</sup></li> <li>• High growth rate<sup>52</sup></li> <li>• Non-Glycosylation<sup>52</sup></li> </ul>	Hecolin® (Innovax) Host: <i>E. coli</i> Disease: Hepatitis E <sup>54</sup>  Trumenba® (Pfizer) Host <i>E. coli</i> Disease: Meningococcal Group B <sup>52</sup>
Insect cells	<ul style="list-style-type: none"> <li>• Medium overall cost<sup>52,53</sup></li> <li>• Medium production time<sup>52,53</sup></li> <li>• Feasible propagation<sup>52,53</sup></li> <li>• High product yield<sup>52,53</sup></li> <li>• Very high scale-up capacity<sup>52,53</sup></li> <li>• Medium product quality<sup>52</sup></li> <li>• Low risk of contamination<sup>52,53</sup></li> <li>• Medium purification cost<sup>52</sup></li> <li>• Good secretion<sup>52</sup></li> <li>• Difficult to cultivate<sup>52</sup></li> <li>• Slow growth rate<sup>52</sup></li> <li>• Good protein folding<sup>52</sup></li> <li>• Glycosylation<sup>52</sup></li> </ul>	Cervarix® (GSK) Host: High Five™ Disease: HPV <sup>54</sup>  FluBlok® (Sanofi Pasteur) Host: ExpressSF+® Disease: Influenza <sup>54</sup>
Transgenic Plants	<ul style="list-style-type: none"> <li>• Low overall cost<sup>52</sup></li> <li>• Medium production time<sup>52,53</sup></li> <li>• Easy propagation<sup>52,53</sup></li> <li>• High product yield<sup>52,53</sup></li> <li>• Very high scale-up capacity<sup>52,53</sup></li> <li>• High product quality<sup>52</sup></li> <li>• Low risk of contamination<sup>52,53</sup></li> <li>• High purification cost<sup>52</sup></li> <li>• Good protein folding<sup>52</sup></li> <li>• Glycosylation<sup>52</sup></li> </ul>	Human plant-based vaccines not yet commercialized <sup>55</sup>
Transgenic Animals	<ul style="list-style-type: none"> <li>• High overall cost<sup>52,53</sup></li> <li>• High production time<sup>52,53</sup></li> <li>• Feasible propagation<sup>52,53</sup></li> <li>• High product yield<sup>52,53</sup></li> <li>• Low scale-up capacity<sup>52,53</sup></li> <li>• High product quality<sup>52</sup></li> <li>• High risk of contamination<sup>52,53</sup></li> <li>• High purification cost<sup>52</sup></li> </ul>	No licensed vaccines <sup>56</sup>

technologies by platform, rather than by individual product, which will expedite the safety aspect of the review, perhaps with accelerated review processes for new indications. For example, the FDA already utilizes this approach for the seasonal flu vaccine.

The United States Food and Drug Administration (U.S. FDA) has shown substantial flexibility in its review of COVID-19 MCMs. Recently, many COVID-19 vaccine developments have combined or overlapped clinical trial phases. While accelerated regulatory processes can enable critical flexibility in an emergency, it is important to weigh the benefits and risks.

#### **5.4. Government support to promote vaccine manufacturing**

There is a vital requirement of demonstrable, long-term political support to enable a country to manufacture vaccines locally. Considerations, for example, could include strong NRA and regulatory infrastructure, policy coherence, incentives, government investment in facility alongside commercial capital, other 'in kind' project support, e.g., provision of low-cost land, HR capacity building through supporting skill development, and supportive business environment.<sup>57</sup>

### **6. Global access challenges with COVID-19 vaccines**

The COVID-19 pandemic has caused a large number of deaths and also impacted the national as well as global economies. Until and unless effective vaccines are administered to large portions of the global population to prevent hospitalization and severe disease, and preferably achieve herd immunity to halt transmission of the virus, the world will not be the same again. Several COVID-19 vaccines have been approved for human use in different parts of the world. But the biggest challenge now will be to produce them at a large scale, pricing them affordably, and allocating them globally so that they are available where needed, and widely deployed in local communities. To suddenly scale up the production to meet global demand is a monumental challenge. In addition, the increasing volume of vaccines will also put pressure on global supply chains for glass vials, syringes, and stabilizing agents. Moreover, prior to this pandemic, there were no established networks of contract manufacturers for candidates using novel technologies like mRNA delivery platforms. The COVID-19 vaccines' production is limited by the highly concentrated state of global vaccine manufacturing capacity, and the established relationships between lead developers and contract manufacturers. A successful solution to the production bottleneck needs widespread technology transfer to enable the expansion of manufacturing capacity. Presently, countries around the world have limited domestic capacity to rapidly manufacture COVID-19 vaccine batches. So, these countries will require global companies to actively share knowledge, technology, and data with domestic manufacturers. LMICs are home to about 85% of the global population and mechanisms will be required to make these vaccines affordable. Universal access of the vaccines to billions of people will be another major challenge in stopping this pandemic in 2021.<sup>58</sup>

### **7. Role of different organizations in capacity building**

Non-governmental organizations (NGOs), institutional organizations, international organizations, charitable donor organizations, and many players in vaccine development and deployment actions in developing countries support capacity building. Examples of organizations working for capacity building in vaccine manufacturing are as follows:

#### **7.1. Bill & Melinda Gates Foundation (BMGF)**

The Vaccine Development and Surveillance team of BMGF invests in expertise and platform technologies that helps in making vaccines faster, better, and affordable. It also ensures that the knowledge around vaccine development and manufacturing is created, shared, and retained through education and training. The aim of the team is advancing public goods for global health through novel technology by accelerating the development and commercialization of innovative vaccines, sustainable manufacturing of existing vaccines, utilizing primary data and world-class modeling to define global disease burden, and using innovative tools to reduce the threat of epidemics.<sup>59</sup>

#### **7.2. Gavi, the Vaccine Alliance (GAVI)**

GAVI, a public-private partnership founded in 2000, helps in vaccinating half of the world's children against some of the world's deadliest diseases. GAVI has vaccinated over 888 million children, averted more than 15 million future deaths and significantly reduced child mortality in 73 lower-income countries. It also plays a crucial role in improving global health security by supporting health systems, as well as funding global stockpiles for Ebola, cholera, meningitis, and yellow fever vaccines. After achieving success in the past 2 decades, it is now focused on protecting the next generation and unvaccinated children using innovative finance and latest technology such as drones and biometrics to save more lives, prevent outbreaks, and help countries in becoming self-sufficient.<sup>60</sup>

#### **7.3. Clinton Health Access Initiative, Inc. (CHAI)**

The CHAI is a global health organization that works toward saving lives and reduction of the disease burden in LMICs. It partners with other organizations to strengthen the capabilities of governments and the private sector to create self-sustained high-quality health systems.<sup>61</sup>

#### **7.4. International Vaccine Access Center (IVAC)**

Based at the Johns Hopkins Bloomberg School of Public Health, IVAC has served as a trusted partner for governments, international agencies, research groups, and non-profit organizations seeking to advance access to life-saving immunizations for all people. It accelerates equitable access to vaccines through the generation, synthesis, and use of evidence to inform decision-making and action.<sup>62</sup>

### **7.5. Coalition for Epidemic Preparedness Innovations (CEPI)**

CEPI, a Norwegian Association, is an innovative global partnership between public, private, philanthropic, and civil society organizations started in Davos 2017 to develop vaccines to stop future epidemics. CEPI accelerates the development of vaccines to prevent emerging infectious diseases and enables equitable access to these vaccines for people during outbreaks.<sup>63</sup>

### **7.6. International Vaccine Institute (IVI)**

IVI is a nonprofit international organization established in 1997 as the United Nations Development Program (UNDP) initiative. It is headquartered in Seoul and hosted by the Republic of Korea with 36 member countries and the WHO on its treaty. It is among the few organizations in the world dedicated to vaccines and vaccination for global health. Its mission is to discover, develop and deliver safe, effective, and affordable vaccines for global public health. IVI aims to make vaccines available and accessible for vulnerable populations in developing countries. It focuses on three components namely research, partnerships, and capacity building.<sup>64</sup>

### **7.7. Netherlands Vaccine Institute (NVI)**

NVI has a stellar track record in the development and transfer of vaccine technology to vaccine manufacturers in both developing as well as developed countries. Noteworthy examples include the transfer of fermentor-based DTwP and BCG technology, as well as the Vero cell-based micro-carrier technology for IPV. The robust Hib conjugate vaccine production process developed by *Rijksinstituut voor Volksgezondheid en Milieu* (RIVM)/NVI and the subsequent technology transfer to vaccine manufacturers in developing countries has helped these countries in getting access to the technology.<sup>65</sup>

### **7.8. The COVID-19 Vaccines Global Access Facility (COVAX)**

COVAX is co-led by CEPI, GAVI, and WHO, alongside key delivery partner UNICEF. In the Americas, the Pan American Health Organization (PAHO) Revolving Fund is the recognized procurement agent for COVAX. Its aim is to accelerate the development and manufacturing of COVID-19 vaccines as well as ensure fair and equitable access of these vaccines to every country across the globe.<sup>66</sup>

## **8. Case studies on capacity building for vaccine manufacturing in developing nations**

There are good examples of how capacity building has helped developing countries to start their own vaccine manufacturing by collaborating with outsourcing organizations.

### **8.1. Collaboration among the Serum Institute of India (SII), GAVI, and the BMGF to accelerate manufacturing and delivery of up to 200 million doses of future vaccines, for low- and middle-income countries in 2021**

Collaboration among SII, GAVI and the BMGF provided an upfront capital to SII to accelerate the manufacturing and delivery of up to 200 million doses of safe and effective COVID-19 vaccines for LMICs as part of the GAVI COVAX AMC, a mechanism within the COVAX Facility.

The ceiling price was capped at US\$3 per dose. This price was enabled by investments made by partners such as CEPI, the BMGF and SII.

The BMGF, via its Strategic Investment Fund, provided further at-risk funding of US\$150 million to GAVI, bringing the total funding to US\$300 million through this collaboration. These funds were used to support SII to manufacture potential vaccine candidates, and for future procurement of vaccines for LMICs via GAVI's COVAX AMC.<sup>67</sup>

### **8.2. Vaccine equity through expanding the geographic distribution of vaccine manufacturing capacity**

In the backdrop of the current pandemic, it was seen that countries with domestic capacity received most of the COVID-19 vaccines, while those without were forced to wait. This highlights the need for expansion of the geographic distribution of vaccine manufacturing capacity.

Vaccine manufacturers located in developing countries (DCVMs) are often more receptive than large multinational corporations to focus on neglected diseases, more so when those diseases remain endemic in a particular country or region. DCVMs play an important role in developing or manufacturing low-cost, high-quality vaccines that can reach everyone. Taking these into considerations, BMGF over the last two decades supported DCVMs with US\$1 billion and worked with 19 DCVMs across 11 countries to bring 17 vaccines to market. These collaborations had a tremendous positive impact all over the world. For example, MenAfriVac, an affordable meningitis conjugate A vaccine was developed by a multi-year partnership with Program for Appropriate Technology in Health (PATH) and the SII. It was the first internationally qualified vaccine developed outside the major multinational pharmaceutical companies' way back in 2010. This vaccine developed specifically for the African meningitis belt has effectively ended meningitis as a public health problem there. Similarly, Euvichol was a low-cost and easy-to-administer cholera vaccine developed by EuBiologics in South Korea. It helped in countering several cholera outbreaks in Africa and prevented further such epidemics all over the world. Indian DCVMs have been particularly successful over the years. Bharat Biotech from India has developed Rotavac, which is an affordable rotavirus vaccine that costs only US\$1 per dose. There are many such examples where DCVMs are making a difference. BMGF is supporting many other DCVMs vaccines in the pipeline. DCVMs now produce more than two-thirds of the vaccine volume for use around the world by GAVI.<sup>68</sup>

### **8.3. International Vaccine Institute (IVI), South Korea, contributed for the successful technology transfer of Vi-DT based typhoid conjugate vaccine (TCV) to SK Chemicals at South Korea, Biofarma at Indonesia and Incepta at Bangladesh**

IVI scientists developed the TCV, by chemically conjugating the Vi polysaccharide purified from *S. Typhi* to diphtheria toxoid (DT). This technology for production and quality control of Vi-DT was transferred to 3 manufacturing partners (SK Chemicals, South Korea; Biofarma, Indonesia; and Incepta, Bangladesh) and worked with them to complete the clinical development with the aim of local licensure and WHO pre-qualification. Among the three, two partner manufacturers (SK Chemicals, South Korea, and Biofarma, Indonesia) have completed phase 1 clinical trials, and Phase 2 clinical trials are currently ongoing.<sup>69</sup>

### **8.4. First successful development of a contemporary recombinant vaccine in Turkey**

Turkey was once totally dependent on imports for her vaccination program. A highly progressive country in terms of public immunization program, Turkey has the most contemporary vaccines in their vaccine schedule. However, 100% of their vaccines were imported and local talent, expertise, and technical know-how were lacking to an extent. The government was facing a shortage of funds to continue importing vaccines for the growing population to support their extensive immunization program. To overcome these challenges, the Turkish ministry mandated one of the renowned universities to set up a novel vaccine development center. After researching all options and avenues, the university approached a resource partner company called Techinvention to help set up Turkey's first vaccine laboratory for indigenous manufacturing of vaccines. The outsourcing company was asked to design the laboratories, train local teams, supervise equipment selection, procurement and installation, transfer the strains/clones, completing technology transfer, and producing successful consistency batches on a pilot scale. The project was started in 2014 and the first successful development of the pilot batches of recombinant Hepatitis B vaccine took place in 2016. This was the first instance for the local development of human vaccine project in Turkey and the effort was well appreciated and covered by media to a large extent.<sup>70</sup>

### **8.5. First vaccine formulation and fill facility in Central America**

There was a joint venture between the governments of Russia and Nicaragua to set up a manufacturing facility for the production of vaccines and other immunological preparations. This venture was Nicaragua's first vaccine manufacturing project and was envisioned to be a future-ready showcase for all the South American nations.

They partnered with a knowledge partner Techinvention, who got involved in executing the entire project. The project began with a futuristic design that helped to stand out from others. Techinvention supported the project from concept to

commercialization and also submitted the feasibility report to secure project funding. The knowledge partner worked with Cuban FDA to ensure vaccine lot release. Techinvention also ensured timely completion of all technology tie-ups for the project and provided the master project plan and basis of design. They also hired an engineering firm to complete the project and also helped with Quality Management System (QMS) implementation. This project started in 2014 and was completed with the establishment of a state-of-the-art manufacturing facility, a first in the region. This unique cross-continent collaboration to help in capacity building development is a model project for other countries to look up to.<sup>70</sup>

### **8.6. Influenza vaccine production capacity building in developing countries: Example of the Serum Institute of India**

SII is one of the largest vaccine manufacturers and has contributed immensely in making India self-sufficient for many basic vaccines. The WHO approached SII for working on capacity building of a pandemic flu vaccine and stockpiling. A special team was created to support the activity of development of the same. The process of development went through handling of simple flu virus strains to seasonal vaccine strains and subsequently H5N1 virus. A suitable system for growing, inactivating, and purifying viruses was developed which could be tailored to facilitate handling of any strain of flu virus to produce a vaccine. SII was able to develop an inactivated adjuvanted H5N1 whole-virus vaccine for animal toxicity studies in the record time of 18–20 months (December 2008). In April/May 2009, reports of a possible swine flu pandemic appeared and subsequently WHO requested SII to develop an H1N1 vaccine. The anticipated challenge was that a stockpile approach alone will not be adequate for countries like India with more than 1.2 billion population. SII looked for technology acquisition which would be highly scalable and offer ease of delivery. A successful agreement was reached between WHO, Nobilon, BioDiam & SII, by which SII obtained the license to use the cold-adapted virus strain for developing an intranasal live attenuated influenza vaccine. In August 2009, the cold adapted strain was received and SII developed Live Attenuated Influenza Vaccine (LAIV) vaccine at an accelerated speed.<sup>71</sup>

### **8.7. Hepatitis B vaccine technology transfer and capacity building in developing countries**

Recombinant hepatitis B vaccines were introduced in industrialized countries by GSK and Merck in 1983. For over a decade, the cost in the region was US\$ 100 per dose, and there was no significant use of the vaccine by developing countries. In the late 1990s, technology transfer to the Republic of Korea, India, and Brazil resulted in a price drop initially to US\$ 5–7 per dose. This increase in supply, the entry of purchasing agencies, and financial assistance from GAVI drove demand up and price down to less than US\$ 0.3 per dose. As a result, the vaccine is now in most national immunization programs, and hepatitis B vaccine coverage is increasing continually.<sup>28</sup>



## 9. The way forward

- **A country in which manufacturing capacity is being built should have appropriate technical skills, QMS, market, and political commitment<sup>24</sup>**

Promising countries that have emerged with a mechanism to address above concerns are India, Colombia, Peru, Brazil, Vietnam, Thailand, China, and Morocco. In collaboration with the United Nations Industrial Development Organization (UNIDO), these countries have augmented the setup for new infrastructure and ramped up existing infrastructure through setting up of dedicated industrial parks.<sup>19</sup>

- **Using advocacy to increase investment in vaccine research and development**

African Vaccine Manufacturer's Initiative (AVMI) advocates to produce vaccines or other biological products against diseases of public health importance, support partnerships between African regional manufacturers of vaccines and biologicals and other stakeholders interested in making Africa self-sufficient in vaccine production, attract and secure skills and financial resources for establishing vaccine manufacturing capacity in Africa and encourage adequate scientific and technical capacity building of Africa's vaccine manufacturers in every aspect of production and distribution of vaccines or other biological products.<sup>72</sup>

- **To generate long-term research interest and subsequent investment from donors in the development of vaccines, scientists need to play an important role in raising awareness of these issues and communicating and disseminating their research**

The Government of India established the Department of Biotechnology in 1986, which led to India establishing its footprints into the world of biosciences and technological advances. Since inception, the department has been focusing on, developing human resources, creation of appropriate infrastructure, research and development, and creating a regulatory framework.<sup>73</sup>

- **Strong collaboration of technology partners and local research institutions**

The WHO and partners launched the COVID-19 Technology Access Pool (C-TAP) to operationalize the Solidarity Call to Action and facilitate timely, equitable, and affordable access to COVID-19 health products. C-TAP, working through its implementing partners (the Medicines Patent Pool, the Open COVID Pledge, and the UN Technology Bank), provides a global one-stop platform for developers of COVID-19 medications, diagnostics, vaccines, and other related products to share their IP knowledge, and data with quality-assured manufacturers through public health-driven voluntary, non-exclusive, and transparent licenses. With the support of WHO and Unitaids, the Medicines Patent Pool temporarily expanded its mandate to cover any COVID-19 related health technologies,

including vaccines and diagnostics.<sup>74</sup> As part of the task force, the WHO established in April 2021, a COVID-19 mRNA vaccine technology transfer hub to scale-up global manufacturing. WHO and its COVAX partners are working with a South African consortium to establish the first COVID mRNA vaccine technology transfer hub.<sup>75</sup>

- **Setting up of regional manufacturing to cater to a number of local countries to make it economically feasible and increase ROI**

The DCVMN aims to protect people against known and emerging infectious diseases globally by increasing the availability of high quality vaccines produced in emerging countries. It works to strengthen vaccine manufacturers through the provision of information programs and professional training on technical improvements, research in vaccine production, encouraging technology transfer initiatives, and educating the public about the availability of safe and effective vaccines, from developing world manufacturers and related programs.<sup>76</sup>

- **Long-term financial planning in terms of infrastructure, and logistics**

Immunization Practices Advisory Committee (IPAC) coordinates with national immunization programs, the Ministry of Health (MOH), and the global community to review and renew investment in their Immunization Supply Chain and Logistics (ISCL) systems. With the introduction of newer vaccines and immunization schedules getting updated, diverse service delivery strategies, expanding target population, increased cold-chain infrastructure requirements, and lack of adequate funds are some of the new challenges for ISCL systems as it was not designed to manage such ever-increasing demands. This has led to stock-outs, potential administration of ineffective vaccines, avoidable wastage, and inadequate cold-chain capacity leading to considerable coverage, performance, and cost implications. These inefficiencies can hinder the ability to provide much-needed immunizations and yield a lower return in health outcomes for those funding the research, production, procurement, and delivery of vaccines, threatening the dependability of future funding sources. The growth in complexity of immunization programs occurs simultaneously with the development and application of innovative supply chain strategies and technology. In the public sector, national immunization programs, and the global community that supports them, have a chance to improve their performance and a mandate to provide the right vaccines in the right quantities, in the right condition, at the right time, in the right place, and at the right supply chain cost.<sup>77</sup>

- **Financing from national governments, venture capitalists (VCs), World Bank, and International Monetary Fund (IMF) to improve manufacturing capability**

The IMF, World Bank (WB) Group, WHO, and World Trade Organization (WTO) are working together to provide access to COVID-19 vaccines, therapeutics, and diagnostics

by leveraging multilateral finance and trade solutions, particularly for LMICs. The mission is to vaccinate at least 40% of people in every country by the end of 2021, and at least 60% by mid-2022. This will involve tracking, coordinating, and advance delivery of COVID-19 vaccines, therapeutics, and diagnostics, working with governments and partners at the global and country levels to solve finance and trade barriers and provide access to these life-saving tools to vulnerable populations. It supports the goals of the Access of COVID-19 Tools (ACT)-Accelerator and complementary initiatives. The Multilateral Leaders Task Force members are facilitating the mobilization of critical financing, focusing on grants and concessional lending, therapeutics, and diagnostics, helping to remove barriers to export and import of vaccines, and supporting more production, including in LMICs. The Task Force is asking countries to share at least 1 billion vaccine doses with developing countries during 2021.<sup>78</sup> Together with the WHO & WTO, the World Bank Group, and IMF have urged international support for 50 billion USD of financing aimed at achieving more equitable access and thus helping to end the pandemic everywhere.<sup>79</sup>

- **Key partnership with government-like public-private partnership and building knowledge partners**

The concept of public-private partnership (PPP) has bridged the gaps between academia, industry, and funding agencies effectively. It integrates the commitment of the public sector to develop products to improve the health of the population with the private sector's discipline and culture in business development and marketing. The nonprofit enterprise has effectively led to the development of several products in the past decade. The PPPs have also evolved innovative methods for IP and portfolio management and have unique governance structures and methods.

The PPP in vaccine research can be strengthened by flexible governing and funding mechanisms that should be evolved to support product development in the PPP model. The flexibility of contracting experts, both from the national and global pool for a defined period should be built-in in these partnerships. While setting up the policy framework, the industry may be provided a channel to voice their opinions and experiences, and their concerns could be utilized in framing the policy. If the industry is genuinely concerned about tardy regulatory mechanisms or a decision has been made to their detriment, an independent and speedy redressal mechanism should be in place. A need-based realistic procurement policy should help. One such example where product development has taken the PPP route and has resulted in a shortening of the time frame for vaccine development is the Meningococcal Meningitis Vaccine Initiative (MMVI). In this initiative, the product was produced in India with multiple partners, met international quality standards, and was exported to, and used in Africa.

Another example is the influenza H1N1 vaccine developed with the support of 3 Indian vaccine manufacturers under the Biotechnology Industry Partnership.<sup>80</sup>

- **Inadequate funding or misuses of funds remain a bottleneck in developing countries**

Timely and adequate availability of funds and robust mechanisms to prevent its misuse remain vital. There have been umpteen instances wherein the funds have been misused. The glaring examples are the misuse of \$563,000 in two of GAVI's cash-based programs in Mali as highlighted by their internal auditors. GAVI had to suspend its cash-based programs in Niger, Cameroon, and Ivory Coast, wherein the misappropriated amount were around \$18 million.<sup>81</sup> Similar case of misappropriation of funds was also observed in Nigeria.<sup>82</sup>

- **The long-term viability of manufacturers need government commitment, policies supporting capital access, and continuous sponsorship of an independent NRA**

For the growth of vaccine manufacturers in many developing countries, the support the manufacturers receive from their governments is very crucial. While overall economic development has helped to increase public and private access to capital, the need for continued capital investment to ensure successful compliance with cGMPs and adoption of new production technology was noted as a particular challenge for manufacturers and important for governments to take into consideration.<sup>31</sup>

A social investor like a country government, a supranational entity, a development finance institution, or a private philanthropy can use a range of financial instruments to encourage greater investment in manufacturing capacity like production subsidy, capacity subsidy, concessional loan, and volume guarantee.<sup>83</sup>

Although all these instruments can incentivize a vaccine developer to enhance its manufacturing capacity, but each intervention results in a different expected cost to the social investor.<sup>83</sup>

These global investments and innovations through worldwide network would better prepare the world for future pandemics and improve equitable access to vaccines around the world. Capacity building for manufacturing of vaccines in developing countries has always been an area that should have been accorded paramount importance. In the COVID-19 scenario and increasing incidences of newly emerging and re-emerging diseases, this arena should be accorded among the highest of importance across strategic initiatives. It goes without saying that while challenges for such initiatives would be plenty, but with meticulous planning, specific stakeholder involvement, and an all-encompassing strategy, such projects not only see the light of the day but also become sustainable, viable, and of national or regional importance.

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