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Sustainable vaccine manufacturing in low- and middle-Income countries

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ABSTRACT

The sustainable manufacturing of vaccines in developing countries is critical to increasing equitable access to vaccines and pandemic preparedness globally. Sustainable manufacturing requires that organizations engaged in the development, production and supply of vaccines have viable business models and incentives to manufacture vaccine products.

The expanding manufacturing capabilities and capacities of developing countries vaccine manufacturers (DCVMs) are increasingly positioning these organizations to meet the national and regional public health needs in developing countries; however, key industry challenges such as regulatory barriers, low prices and demand uncertainty for vaccine products, and limited R&D funding threaten the long-term viability of vaccine manufacturers.

This study assesses the technical capabilities, manufacturing capacities, and aspirational plans of DCVMs, exemplifying the business models and strategies undertaken to sustainably manufacture vaccines in developing countries. The public health importance of a healthy vaccine industry which enables manufacturers is discussed throughout.

Vaccine manufacturers reported diverse product portfolios and R&D pipelines and utilized an array of vaccine technology platforms. Large manufacturing capacities were reported, a critical factor in manufacturers achieving economies of scale and supplying large volumes of vaccine doses to the world's most populous regions. Partnerships and collaboration within the industry and with international organizations along the vaccine value-chain were cited with high frequency. Manufacturers also reported aspirational plans to enter new markets, acquire new technologies and invest in the development of novel and improved vaccines.

As DCVMs aim to have an increasing impact on the global vaccine ecosystem, a coordinated multi-stakeholder approach is required alleviate critical industry barriers to ensure that all efforts produce vaccines are sustainable and enable developing countries to realize the public health benefit of vaccines.

1. Introduction

Vaccines are one of the most effective interventions in public health. It is estimated that immunization saves 4–5 million lives annually and protects millions more from illness and disability [1]. Additionally, immunization has critical positive economic and societal benefits [2]. Despite these benefits, vaccines as public health tools remain underutilized. In 2020, global vaccine coverage was 83 %, with 23 million infants not receiving basic vaccinations [3]. The World Health Organization (WHO) estimates that 1.5 million people lose their lives to vaccine-preventable diseases each year [1]. The underutilization of vaccines results from the intricacies associated with the development, production, supply, acceptance, and administration of vaccine products globally. This study primarily focuses on the complexities pertaining to the development, production, and supply of vaccines in low- and middle-income countries (LMICs) – nations that experience the highest health economic burden of diseases given the proliferation of infectious diseases and limited medical infrastructure in these countries [4]. Specifically, we evaluate the role of developing country vaccine manufacturers (DCVMs) in contributing to the sustainable manufacturing of vaccines globally, and the critical role of international stakeholders in supporting a healthy ecosystem which demands that vaccines are optimally utilized to protect all people from known and emerging infectious diseases.

Sustainable vaccine manufacturing necessitates continuous development, production, and supply of safe, effective, and afford-

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able vaccines globally. In this context, organizations must have viable business models and incentives to manufacture vaccine products. Due to the complexities and costs associated with vaccine development, production, and supply remaining viable is an arduous task resulting in organizations exiting the industry and facilities closing [5]. The subsequent industry consolidation is a departure from the competitive market paradigm and contributes to an underperforming industry [6]. The consequences of an underperforming industry, such as vaccine shortages, industry exits, and underinvestment in research and development (R&D) are often disproportionately borne by LMICs [6]. To address the inefficiencies undermining the vaccine industry, various governments, non-governmental organizations (NGOs), and multilateral organizations are required to intervene so that the public health benefits of vaccines can be realized [7]. Stakeholder interventions are primarily targeted towards improving health outcomes in LMICs, which are most at risk of infectious diseases. As these nations also have the lowest ability to pay for vaccine products, such interventions have the greatest public health impact. For example, immunization in LMICs is estimated to avert 69 million deaths between 2000 and 2030 [8].

A fundamental issue contributing to the burden of infectious diseases is that multi-national corporations (MNCs), which dominate the industry's market share, often lack the incentives to develop, produce and supply vaccines for LMICs [7,9]. This misalignment has fueled the growth of DCVMs in producing affordable vaccines in large volumes for domestic and global supply [10]. Furthermore, DCVMs have increasingly been engaged in developing innovative vaccines that improve health outcomes in LMICs [11].

DCVMs produce the bulk of vaccines supplied globally yet retain a small proportion of the global market share [6,12], partly due to low prices demanded by national governments in LMICs and procurement agencies. In such a market environment, to remain viable DCVMs need to achieve economies of scale and scope, necessitating strong technical capabilities and sufficient market demand (either through large domestic markets or exports). These factors, among others, pose a challenge to the viability of existing and emerging DCVMs, putting supply security and equitable vaccine access at risk [13–15]. The preexisting challenges faced by the vaccine industry and their public health consequences were made evident during the COVID-19 pandemic [16]. Notable, the pandemic has highlighted the global inequity in access to vaccines and the risk to national and regional health security when vaccine manufacturing facilities and expertise are geographically concentrated [17].

To better understand the geographical distribution of vaccine manufacturing capabilities and capacities across LMIC global regions, the Coalition for Epidemic Preparedness Innovations (CEPI),[1] conducted a survey, mapping the vaccine manufacturing landscape in Africa, the Middle East, Latin America, South-East Asia, and Western Pacific regions. This study critically assessed existing regional capabilities and identified gaps and opportunities to enhance vaccine access and pandemic preparedness globally [18].

Underpinning any strategy to increase global and equitable access to vaccines is ensuring that manufacturers in developing countries are capable of sustainably developing, producing, and supplying vaccines. Building on the findings of CEPI's landscaping survey, this paper offers an in-depth assessment of the prevailing capabilities, supply channels, development modes, support received and aspirational plans of a subset of established developing country vaccine manufacturers (DCVMs) that are members of the Developing Countries Vaccine Manufacturers Network (DCVMN).[2]

The study finds that DCVMs have diverse product portfolios, R&D pipelines, and utilize an array of technology platforms. Manufacturers reported supplying large volumes of vaccines to domestic markets; however, many manufacturers are also actively exporting vaccines internationally through country approvals or UN procurement mechanisms. High rates of partnerships and funding support, particularly for vaccine development, were reported. Findings indicate that DCVMs are successfully able to access intellectual property (IP), acquire new technologies and scale-up vaccine production – all critical to their development in a competitive global vaccine industry. Furthermore, manufacturers reported strategic plans to expand manufacturing capabilities and capacities and access new markets.

The capabilities of DCVMs provide a strong foundation to yield optimal public health benefits in LMICs. However, the complexity of vaccine manufacturing and market inefficiencies present many challenges. In the context of several industry challenges, we discuss the strategies of DCVMs and the multi-stakeholder approach that is required to overcome these barriers and help enable a healthy vaccine industry.

2. Methods

To better understand the ability of DCVMN companies to support the sustainable supply of high-quality, affordable vaccines globally, an online 41-question survey was used. All 42 DCVMN member companies were invited to respond to the online survey, which was circulated, by email, on the November 19th, 2021. A total of five reminders were periodically sent to maximize participation. The final reminder was sent on January 10th, 2022, with the last response being received on January 17th, 2022.

The survey comprised of 41-questions covering six topics: company profile; vaccine manufacturing capacity and capabilities; supply channels and market access; partnerships and technology acquisition; support and funding mechanisms; and an assessment of the barriers to sustainable manufacturing. At the beginning of the survey, the following information was given: the purpose of the questionnaire, background information and instructions, and an assurance of proper handling of confidential information.

The survey primarily consisted of close-ended questions with a set of pre-defined responses e.g., checklists or yes/no questions, to facilitate the descriptive statistical analysis. Some close-ended questions, did however, include the option 'Other – please specify' to collect inputs and insights which were not on the pre-selected list of responses. For questions in which numeric data entry was required units were clearly specified to minimize measurement error. The survey questions are provided in the supplementary material (Appendix A). Furthermore, where appropriate, table and figure legends detail the survey question structure which generated the data shown in the outputs.

Survey responses were manually entered into a database and any duplicates were removed. The survey responses to each question were analyzed descriptively, generating the statistics (arithmetic means, sums, and percentages) which are presented in this report. The responses to each question were aggregated to include all respondents that completed the given question and to ensure the confidentiality of sensitive information. When applicable, results are reported based on the geographical location of the manufacturers.[3]

[1] https://cepi.net/.
[2] https://dcvmn.net/.
[3] Manufacturers were grouped by WHO Regions. https://www.who.int/about/who-we-are/regional-offices.

To contextualize the findings of this study and empower the studies discussion points and conclusions, a search for relevant literature was conducted. The search strategy and criteria are detailed in the supplementary material (Appendix B).

3. Results

Overall, 26 of the 42 DCVMN member companies responded to the survey, representing a response rate of approximately 62%. Survey respondents represent vaccine manufacturers from five WHO regions: Africa, Americas,[4] Europe, South-East Asia and Western Pacific, with the majority being based in the South-East Asia and Western Pacific regions (Fig. 1A). Additionally, respondents represent a mix of private, public, and state-owned manufacturers (Fig. 1B).

3.1. Vaccine manufacturing capabilities

Developing country vaccine manufacturers (DCVMs) reported diverse product portfolios and R&D pipelines. Furthermore, manufacturers reported utilizing an array of technology platforms.

Overall, manufacturers reported producing, on average, almost four vaccine products in 2021 (Fig. 2A). Manufacturers from WHO's Americas region, on average, reported the most diverse product portfolios, producing six commercial products in 2021.

DCVMs, on average, have almost five candidates in the R&D pipeline with most vaccine candidates in pre-clinical development or Phase III trials (Fig. 2B). COVID-19 and pneumococcal conjugate vaccines (PCV) were the most common vaccines in R&D, followed by DTaP, seasonal flu, and HPV vaccine candidates (Table 1). Multiple manufacturers are also engaged in the development of novel vaccines for Zika, RSV, and chikungunya, in addition to needed next-generation vaccines for tuberculosis.

This study identified that DCVMs actively utilize, on average, almost four vaccine technology platforms (Fig. 2A). Manufacturers reported primarily utilizing traditional technology platforms

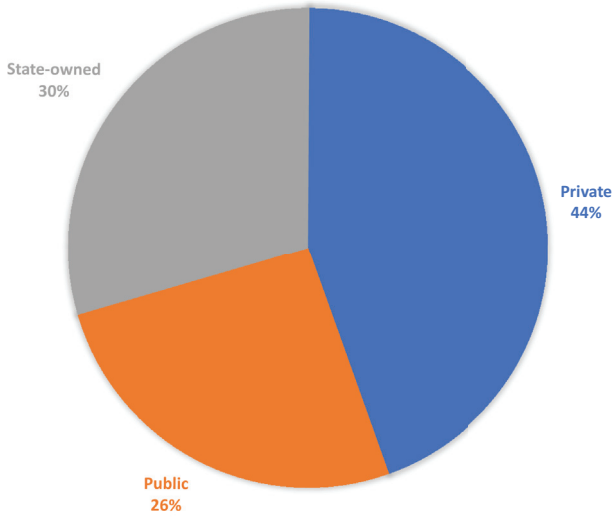

Fig. 1B. Summary statistics of survey respondents. A breakdown of the ownership structure of the manufacturers which responded to the survey. 26 DCVMN members voluntarily responded to the survey.

(Fig. 2C). While utilization of specific modern technologies is less frequent among DCVMs, results reveal that almost half of all manufacturers currently utilize at least one of the following modern vaccine technology platforms: viral vectors (replicating and non-replicating), DNA, and mRNA. Western Pacific (WPR) and South-East Asia Region (SEAR) manufacturers reported the highest usage of modern vaccine technology platforms (Fig. 2D).

Aggregating the average number of vaccine products, pipeline candidates and technology platforms in each region provides a measure of manufacturing capabilities. As illustrated in Fig. 2A, this index illustrates strong and well-balanced regional capabilities among DCVMs for these chosen parameters.

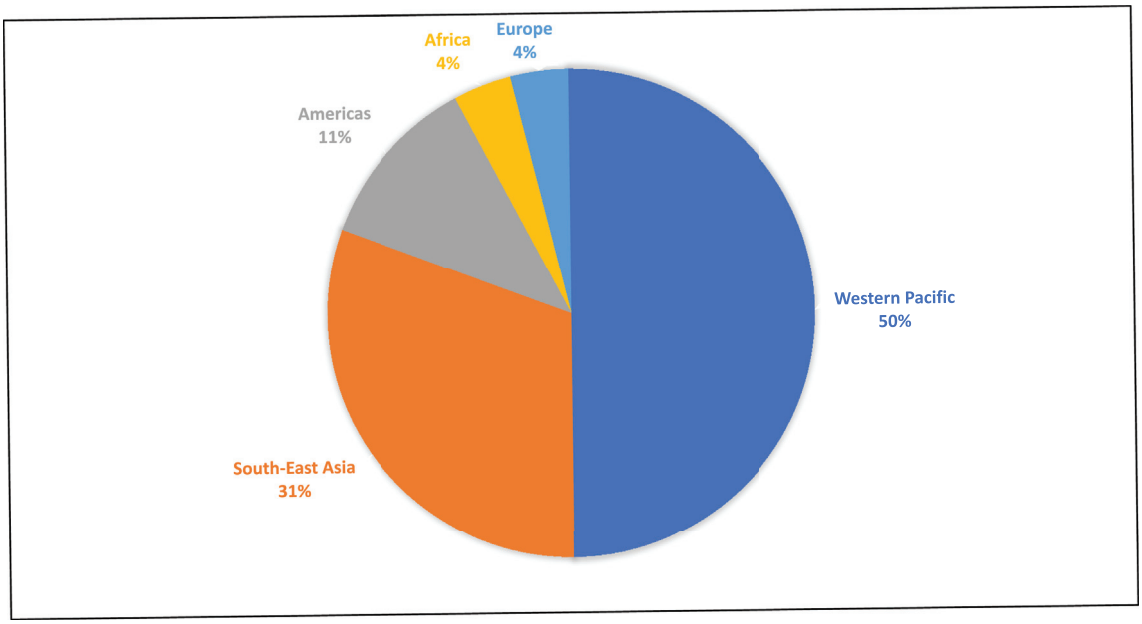

Fig. 1A. Summary statistics of survey respondents. A breakdown of the geographical location (based on WHO regions) of survey respondents. 26 DCVMN members voluntarily responded to the survey: one from WHO Africa, one from WHO Europe, three from WHO Americas, eight from WHO South-East Asia, thirteen from WHO Western Pacific. 16 DCVMN members did not respond to the survey: one from WHO Africa, one from WHO Europe, two from WHO Eastern Mediterranean, seven from WHO South-East Asia, five from WHO Western Pacific. Consequently, the percentage of DCVMN members from each WHO region that responded is as follows: Africa (1/2 – 50%), Americas (3/3 – 100%), Eastern Mediterranean (0/2 – 0%), Europe (1/2 – 50%), South-East Asia (8/15 – 53%), Western Pacific (13/18 – 72%).

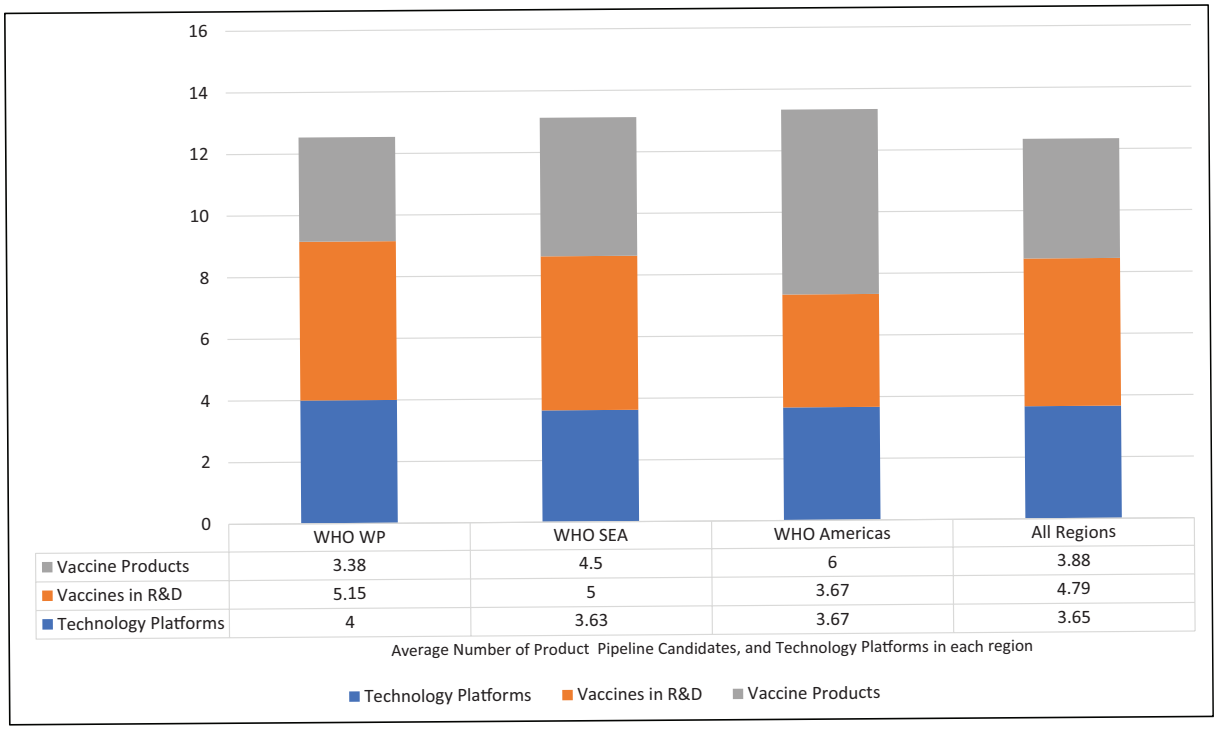

Fig. 2A. Regional assessment of manufacturer capabilities. The average number of vaccine products, vaccines in R&D, and technology platforms utilized by manufacturers in the following geographical regions: Western Pacific, South-East Asia, and Americas. Vaccines in R&D includes candidates in both pre-clinical, phase I, phase II, and phase III clinical development. Vaccine products includes those products produced in 2021. Technology platforms are those that are currently being utilized by the manufacturer at the time of the survey. The average number of vaccine products, vaccines in R&D, and technology platforms are aggregated to measure the regional capabilities of manufacturers. The final column considers all manufacturers, including the two manufacturers that are not located in the Western Pacific, South-East Asia, or Americas region (located in WHO Africa and WHO Europe).

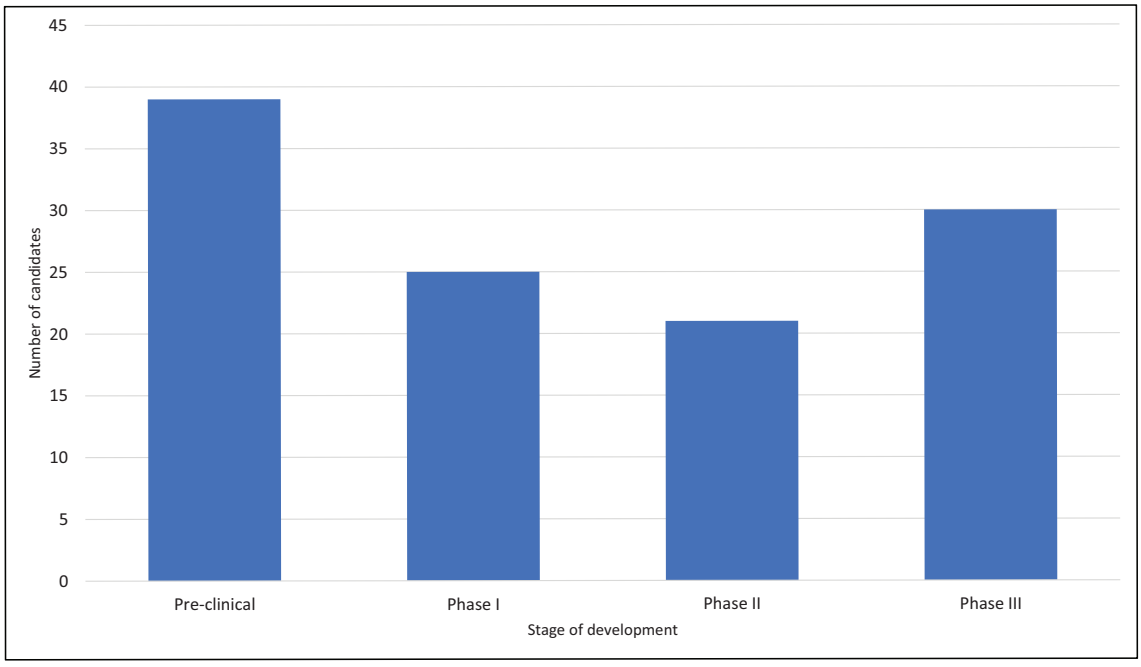

Fig. 2B. Research & development (R&D) pipeline of manufacturers. Respondents were requested to list their vaccine candidates in each stage of development. Overall, 24 manufacturers (92.3% of survey respondents) stated having capabilities in vaccine R&D. Of the 24 manufacturers, 22 companies shared their vaccine development pipeline. The remaining two companies are either not currently active in vaccine R&D or did not share their vaccine pipeline for reasons of confidentiality. During the study period (November 19th, 2021 – January 17th, 2022) survey results identified that a total of 115 candidates are under development: 39 (30%) are in pre-clinical development, 25 (22%) are in Phase I, 21 (18%) are in Phase II, and 30 (26%) are in Phase III.

Table 1
The most common vaccine candidates being developed by manufacturers. The number of pipeline candidates for the different vaccine types is provided. Several manufacturers have multiple candidates for the same vaccine type. For example, 13 manufacturers have a total of 18 COVID-19 vaccine candidates in the research and development (R&D) pipeline.

Vaccine Candidate(s)	Number of candidates currently in DCVMs R&D pipelines
COVID-19	>15
PCV	10–15
DTaP, HPV, Seasonal Flu	5–9
Zoster, Zika, IPV, Men ACYW, EV-71, Tuberculosis	3–4
Men B, Hib, Rabies, DTaP-Hib, Rotavirus, Hep B, Hep E, TCV, mOPV	2

3.2. Manufacturing capacities

Our survey findings confirm extant knowledge of production capacities in developing countries. The average reported production capacity was 294 million doses, and four manufacturers reported capacities of greater than one billion doses (Fig. 3A). On average, the largest manufacturing capacities were reported in the SEAR, with facilities having an average capacity of over 500 million doses per annum. Average capacities among WPR facilities were almost 300 million and in the Americas region, DCVMs reported an average production capacity of 170 million doses (Fig. 3B).

To evaluate how active manufacturers facilities were in 2021, the aggregate number of doses produced annually was measured against the aggregate annual production capacity. Overall, approximately 42% of manufacturers production capacity was used to produce vaccine doses in 2021. The underutilization of facilities was most evident in the WPR. The Americas were the only region in which facilities were operating at near capacity (96%) (Fig. 3C).

3.3. Vaccine distribution and market access

DCVMs are primarily focused on supplying domestic markets. 95% of manufacturers reported supplying vaccines domestically and domestic supply comprised 65 % of all vaccine doses produced in 2021 (Fig. 4A). Two-thirds of manufacturers supplied vaccines internationally and 40 % supplied vaccine products to UN procurement agencies, requiring WHO pre-qualification (PQ) (Fig. 4A). Approximately 31% of all doses produced in 2021 were supplied internationally, 17% specifically being procured by UN agencies (Fig. 4A).

Focusing on the income levels of the countries supplied by DCVMs, a large proportion of manufacturers supply vaccines to LMICs – likely reflecting manufacturers domestic supply and vaccine procurement by UN agencies. Supply to middle-income countries (MICs) that are not eligible for GAVI funding is less pervasive, with only 44% of manufacturers supplying these markets. 20% of manufacturers reported supplying vaccines to high-income countries (Fig. 4B).

3.4. Partnerships and acquiring new vaccine technologies

To develop, produce, and supply vaccine products, partnerships at different stages of the value chain are critical. The most common form of partnership employed by DCVMs are licensing agreements, with over 90% of the manufacturers currently engaging in this form of partnership (Fig. 5A). Manufacturers also reported active engagement in product development partnerships (PDPs) (62%). Other forms of partnership were less frequently reported yet occur at high rates highlighting the importance of partnerships in vaccine manufacturing (Fig. 5A). Furthermore, the manufacturing processes for which DCVMs engaged in licensing agreements and joint ventures were assessed. Licensing agreements were most used in R&D and for fill-finish operations while, joint ventures, albeit less

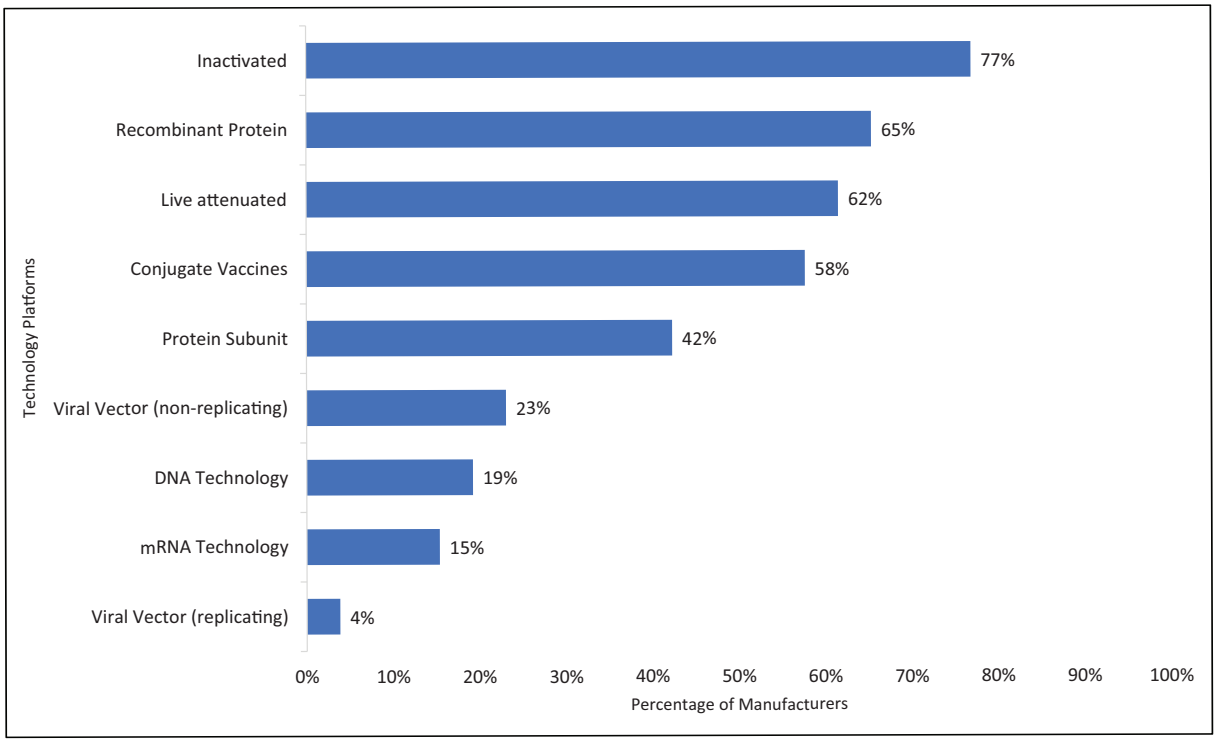

Fig. 2C. Utilization of technology platforms. The percentage of manufacturers which currently utilize the listed technology platforms is given. Respondents were requested to selected from a predefined list of nine pre-selected vaccine technology platforms.

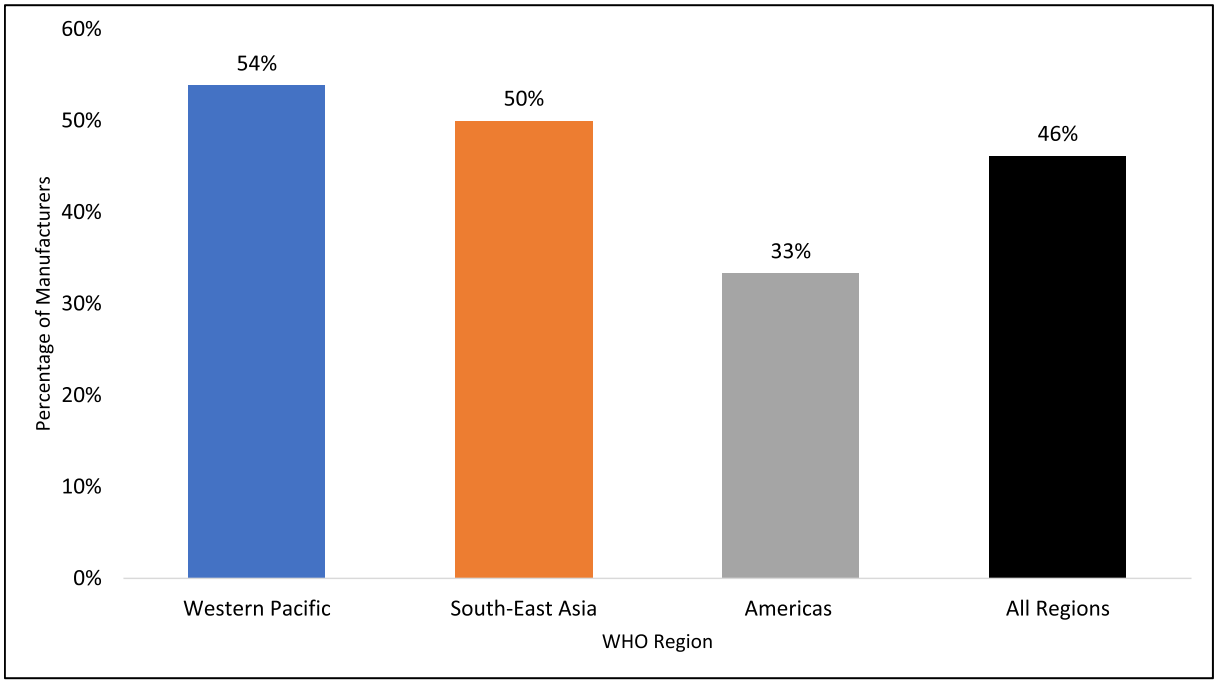

Fig. 2D. Utilization of modern technology platforms. Percentage of manufacturers in different geographical regions that utilize at least one modern technology platform. In this analysis, viral vectors (replicating and non-replicating), DNA, and mRNA are considered modern vaccine technology platforms. For example, 54% of manufacturers in the Western Pacific region currently utilize a modern technology platform. The final column considers all manufacturers, including the two manufacturers (located in WHO Africa and WHO Europe) not in the Western Pacific, South-East Asia, or Americas regions.

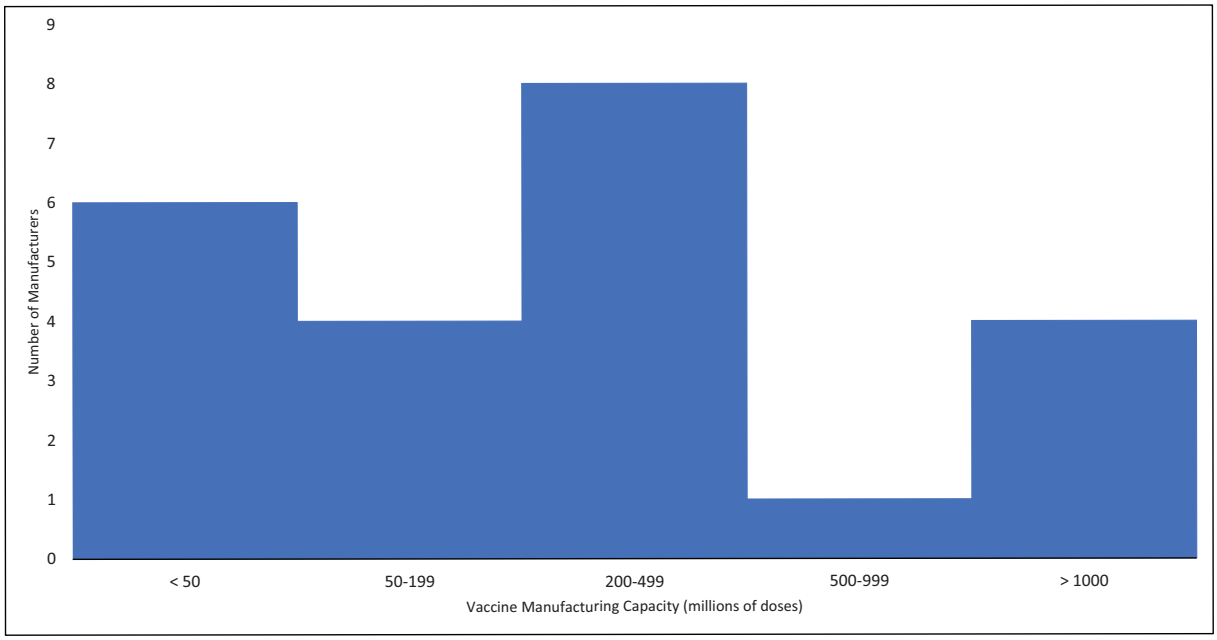

Fig. 3A. Vaccine manufacturing capacities. 23 of the 26 survey respondents (88.5%) shared the annual vaccine manufacturing capacities of their facilities, in millions of doses. The average annual manufacturing capacity of survey respondents was 294 million doses per manufacturer. More than half (57%) of the manufacturers reported manufacturing capacities of greater than 200 million doses. *two of the responding manufacturers shared their total number of doses produced in 2021 but not their annual manufacturing capacity. In this case the total number of doses produced was used as a proxy for annual manufacturing capacity.

common, were most used for drug product and fill-finish manufacturing (Fig. 5B).

Our results found that the most common types of partners for the manufacturers were academic institutions, small biotechnology companies and multilateral agencies (Fig. 5C).

3.5. Acquiring new vaccine technologies

For the majority of DCVMs, new technologies were acquired through technology transfer mechanisms – with 81% of manufacturing acquiring new vaccine technology through tech transfer in

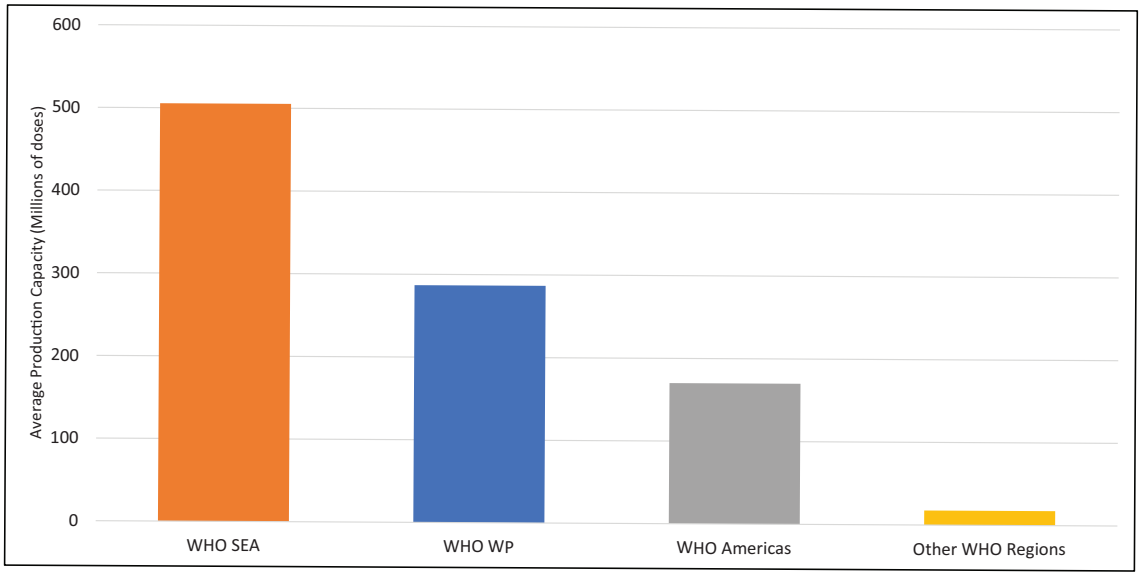

Fig. 3B. Average production capacity of manufacturing facilities in geographical regions. A geographical breakdown of average annual vaccine manufacturing capacities, in millions of doses.

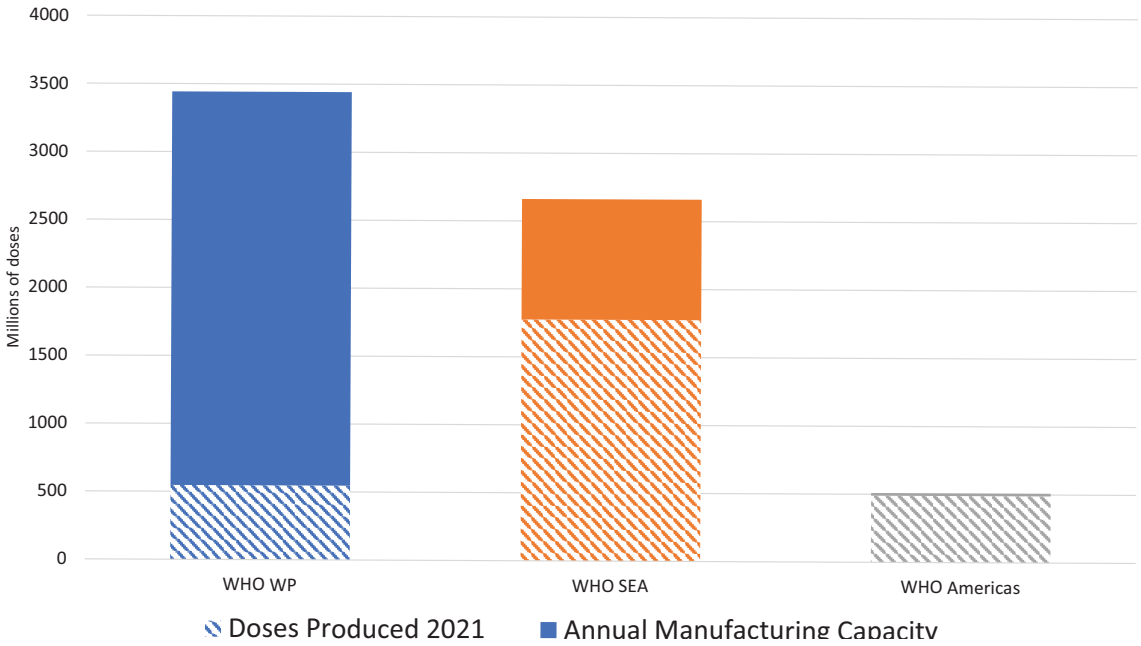

Fig. 3C. Number of vaccine doses produced in 2021 vs total production capacity. 21 of 26 survey respondents (80.8%) shared both the number of doses produced in 2021 and their annual manufacturing capacity. The columns indicate the total production manufacturing capacity, with the shaded area indicating the total number of doses produced in 2021, in the listed regions. The figure illustrates data provided by twelve Western Pacific manufacturers, five from South-East Asia, and three from the Americans region. The figure illustrates how active facilities were in 2021. Overall, the total number of doses produced equates to 42.4% of the manufacturers total manufacturing capacity. The large difference between doses produced in 2021 and annual production capacity may reflect that many manufacturers have up-scaled their production capacity in 2021. This additional capacity may not have been actively producing vaccine doses for the full year.

the past five years (Fig. 5D). Given that tech transfers can be a long and costly process, DCVMs can elect to develop new technologies internally. Approximately 69% of manufacturers reported developing new technologies internally (Fig. 5D). Overall, in the past five years all manufacturers acquired new vaccine technologies (Table 2). Additionally, in evaluating the progress of DCVMs in the past five years it is worth noting that over 80% of manufacturers have scaled-up manufacturing capacity and almost 85% have accessed intellectual property (Table 2).

3.6. Support mechanisms for vaccine manufacturing

DCVMs require monetary and non-monetary support to address the inefficiencies inherent to the vaccine industry and to maximize

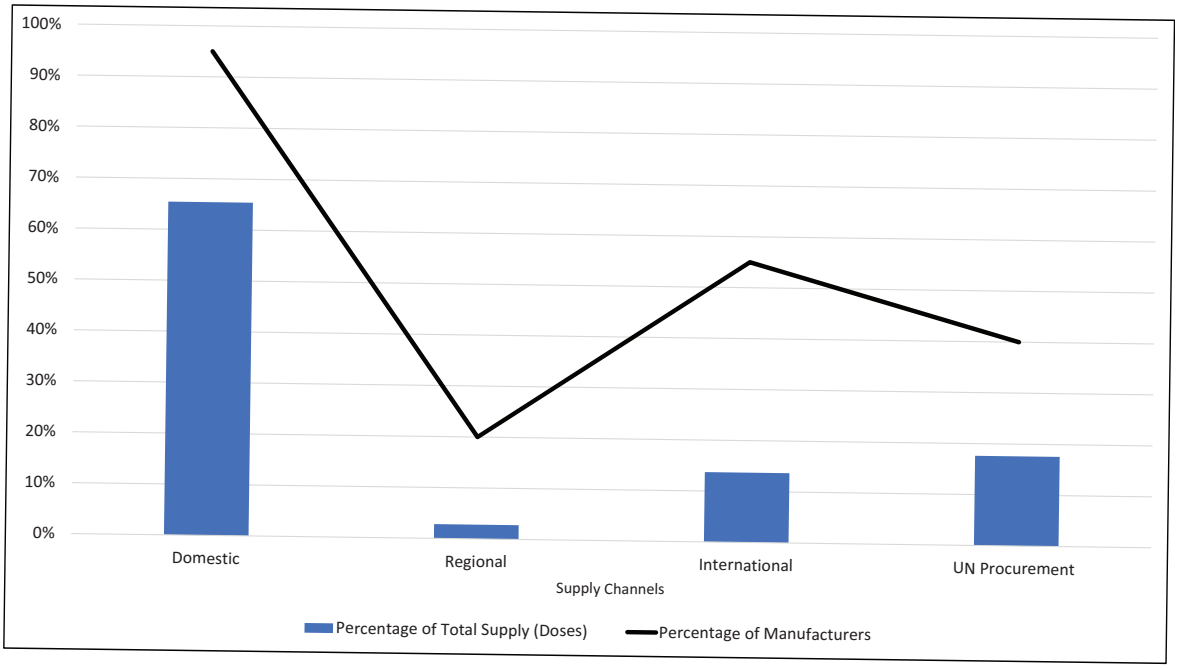

Fig. 4A. Vaccine supply channels. Analysis based on information provided by 20 manufacturers who disclosed both the total number of doses produced in 2021 and the percentage of doses that were supplied through the preselected listed channels. Blue columns indicate the percentage of total doses produced in 2021 and supplied through the given channel. For example, approximately 65% of all vaccine doses were supplied to domestic markets. The black line indicates the percentage of manufacturers which supply vaccines through the given channel. For example, 95% of manufacturers supply vaccines domestically while 40% supply vaccines to UN agencies.

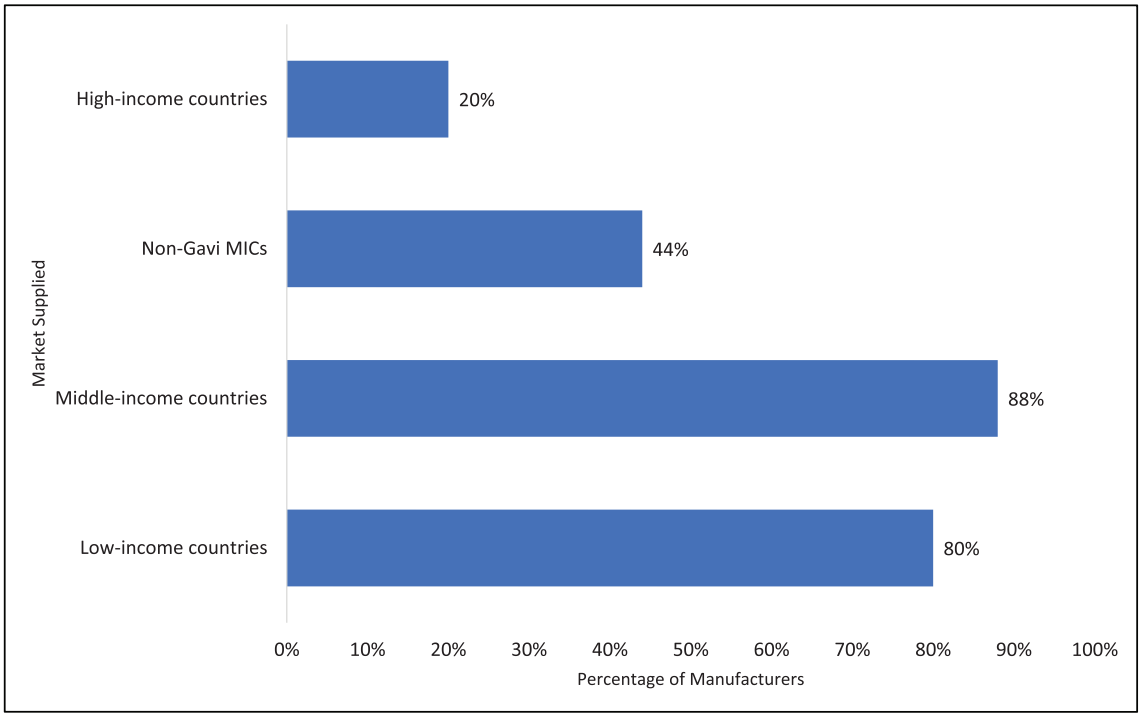

Fig. 4B. Markets supplied by manufacturers. The percentage of manufacturers which reported supplying vaccine products to the preselected listed markets.

the social benefits immunization can provide. In our study, over 73% of manufacturers reported receiving funding from their national government. Additionally, 42% of manufacturers received funding from international organizations (Fig. 6A). While monetary funding has primarily been dedicated to the clinical development of vaccine candidates, many manufacturers also reported receiving funding for pre-clinical development and to scale-up manufacturing capacity (Fig. 6B).

Our study found that non-monetary support was less commonplace relative to funding support. 31% of manufacturers reported

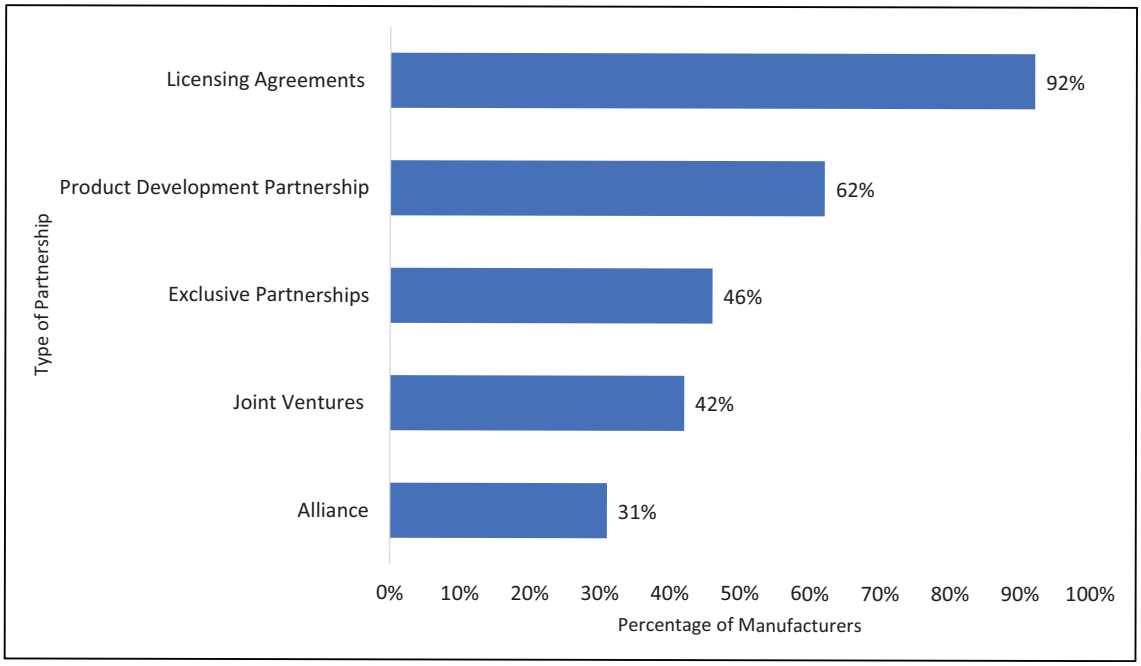

Fig. 5A. Partnerships and licensing agreements to develop and/or produce vaccines. Percentage of manufacturers engaging in the preselected listed forms of partnership to develop and/or produce vaccines.

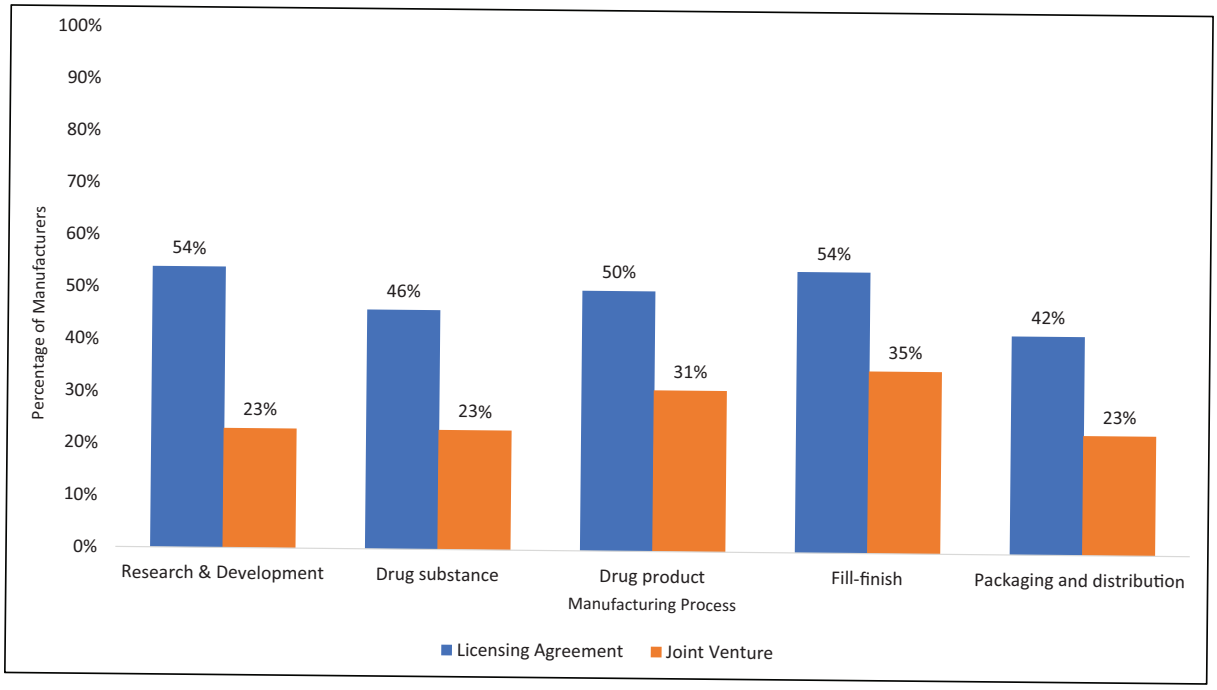

Fig. 5B. Manufacturing processes for which manufacturers engage in licensing agreements and/or joint ventures. Percentage of manufacturers engaging in licensing agreements and/or joint ventures for the preselected listed manufacturing processes.

receiving non-monetary support from international organizations. Support was also provided by governments and academic institutions (Fig. 6A).

3.7. Manufacturers aspirational plans

We observed that almost 90% of manufacturers had strategic plans to acquire a new vaccine technology in the next five years, with technology transfers being the most cited intended acquisition mechanism. Furthermore, over 90% of manufacturers reported plans to scale up their manufacturing capacities. Lastly, 85% of manufacturers reported the intention to engage in the development of novel and improved vaccines (Table 2).

3.8. Barriers to sustainable manufacturing

To better understand the challenges DCVMs face in sustainably manufacturing vaccines, inputs on the most critical barriers, as

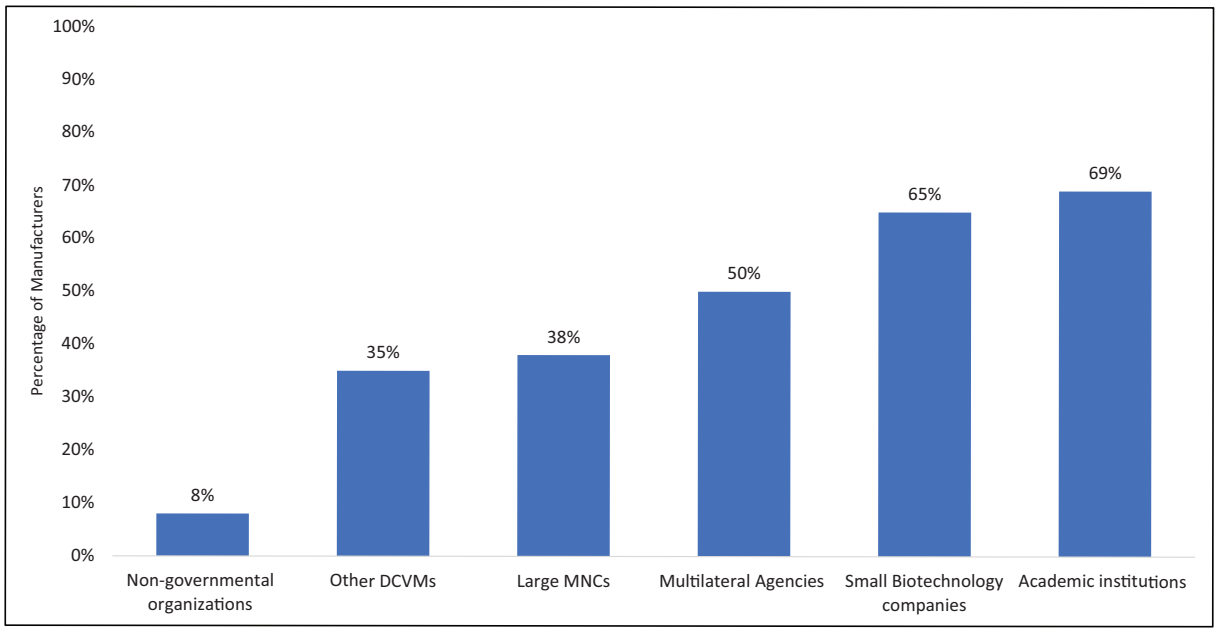

Fig. 5C. Partners of manufacturers. Percentage of manufacturers which have partnerships (including licensing agreements, joint ventures, alliances, PDP, and exclusive partnerships) with the preselected listed types of organizations.

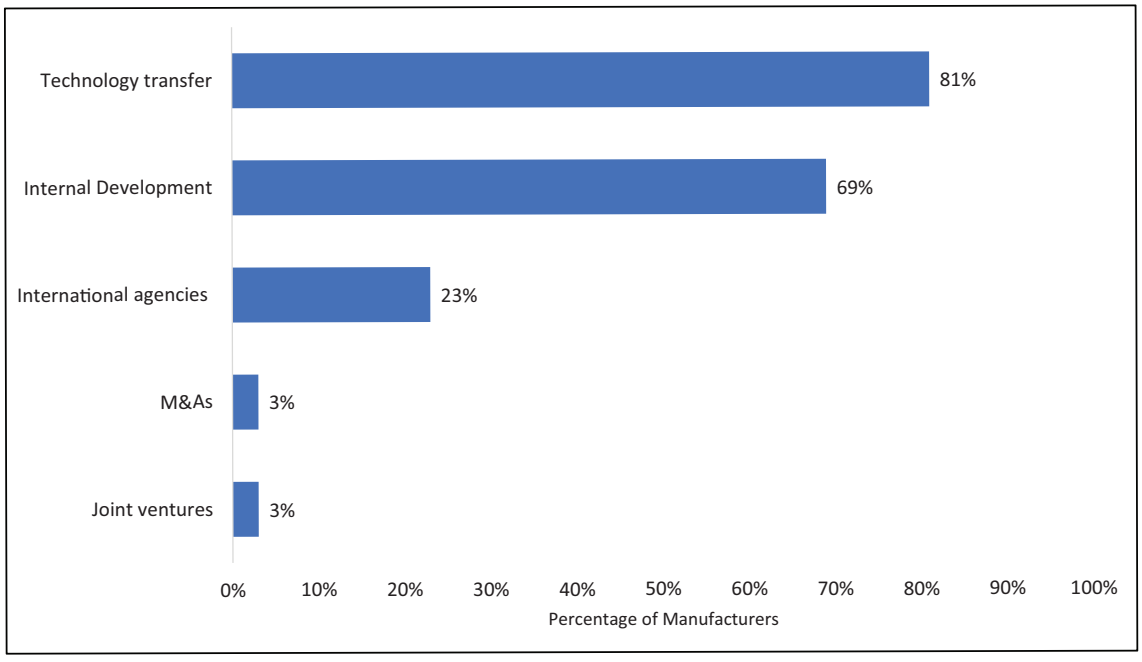

Fig. 5D. Mechanisms to acquire new manufacturing technologies. Percentage of manufacturers who have acquired a new manufacturing technology in the last 5 years by the preselected listed mechanisms.

selected by manufacturers themselves, were sought. Our results found that regulatory challenges were the most critical barrier to sustainably manufacturing vaccines. Low prices, demand uncertainty and limited capabilities to expand to new markets were also cited frequently by manufacturers (Fig. 7A).

When considering the vaccine industry globally, manufacturers listed lack of regulatory harmonization as the most critical barrier. Manufacturers also cited limited investment in novel and improved vaccines, price competition, and demand uncertainty as critical barriers to sustainable manufacturing (Fig. 7B).

4. Discussion

4.1. Diverse manufacturing capabilities for public health good

The production of multiple vaccine products is technically complex, yet it is a proven mechanism to mitigate the high fixed costs associated with manufacturing vaccines [5]. Large volumes spread the high fixed costs of vaccine development and establishing facilities – a business model employed by many DCVMs. While large production capacity of a single vaccine reduces costs over the

Table 2
Overview of manufacturers growth and aspirational plans. Percentage of manufacturers that have achieved the listed advancements in the past five years. Percentage of manufacturers that currently have a strategy to undertake the listed activities in the next five years. Respondents were requested to answer 'yes' or 'no' to the questions.*Novel vaccines: new vaccines for diseases with no approved vaccines yet (e.g., Chikungunya, Zika, HIV). Improved vaccines: vaccines which offer additional value over existing products in terms of antigen attributes, thermostability, and/or presentation (e.g., rotavirus, pneumococcal vaccine).

In the past 5 years		In the next 5 years	
Advancement	Percentage (%)	Strategic Plan	Percentage (%)
Acquired at least one technology platform	100	Acquire at least one new technology platform	88.5
Scaled-up vaccine manufacturing capacity	80.8	Scale-up vaccine manufacturing capacity	92.3
Accessed intellectual property	84.6	Engage in development of novel and/or improved vaccines	84.6

products lifecycle, a mono-product company is vulnerable to demand uncertainties and new entrants to the market. To be viable, it is suggested that DCVMs have a product portfolio with at least two approved products [13]. Furthermore, while a vaccine product generally requires its own dedicated facility and staff, many inputs (human and physical capital, technology) are substitutable across manufacturing processes for different products, resulting in economies of scope and protection from demand shocks [5]. Due to these factors, the sustainability of DCVMs is inherently tied to their ability to produce volumes sufficiently large to spread the high fixed costs of vaccine manufacturing (economies of scale) and capabilities in producing multiple products, to circumvent market uncertainty and benefit from economies of scope.

Furthermore, increased product availability is critical to the sustainable supply of vaccines to meet global health needs. The presence of competitive markets, consisting of multiple producers of a given vaccine product increases access and minimizes the risk of global shortages. Moreover, the introduction of vaccine products by DCVMs has been and will continue to be instrumental in increasing the affordability of vaccine products globally [14]. A key mechanism which enables DCVMs to supply affordable vaccines globally is the WHO PQ system. A vaccine product with WHO PQ is eligible for procurement by United Nations (UN) agencies, which facilitates access to high-quality and affordable vaccines globally [19]. As of March 18th, 2022, 79 vaccine products from 16 DCVMN member companies have WHO pre-qualification [20].

Various technology platforms are used in vaccine manufacturing, with each platform having its respective advantages and drawbacks [21]. The benefits of mRNA technology for the rapid development and scaled production of vaccines prompted strong interest from DCVMs to acquire the technology [22,23]. Efforts are in place to enhance access to this technology; notably the WHO is in the process of establishing regional mRNA technology transfer hubs to facilitate the adoption and effective utilization of mRNA technology [24,25]. The acquisition of new technologies and technical know-how is critical to the growth of DCVMs; however, this must complement traditional platforms that have been proven to produce effective vaccine products. Modern technology platforms remain mostly unverified – currently the only licensed vaccines using mRNA platforms are COVID-19 vaccines [26]. Therefore, existing and emerging manufacturers should not have a reliance on a single modern platform. Rather, manufacturers should attain broad capabilities in utilizing one or more platforms to produce multiple distinct vaccine products. DCVMs should leverage existing vaccine technologies to produce multiple vaccine while actively engaging in mechanisms to acquire potentially disruptive innovative technologies such as mRNA technology [27,28].

The public health benefit of DCVM's diverse capabilities in utilizing vaccine technology platforms was apparent during the COVID-19 pandemic. Successful COVID-19 vaccine candidates were developed using several different technology platforms; hence DCVMs were well-positioned to scale up the production of different COVID-19 vaccines. Experience in using the technology platforms employed by vaccine developers and the technical capabilities to rapidly repurpose manufacturing facilities for COVID-19 production permitted several DCVMs to partner with developers

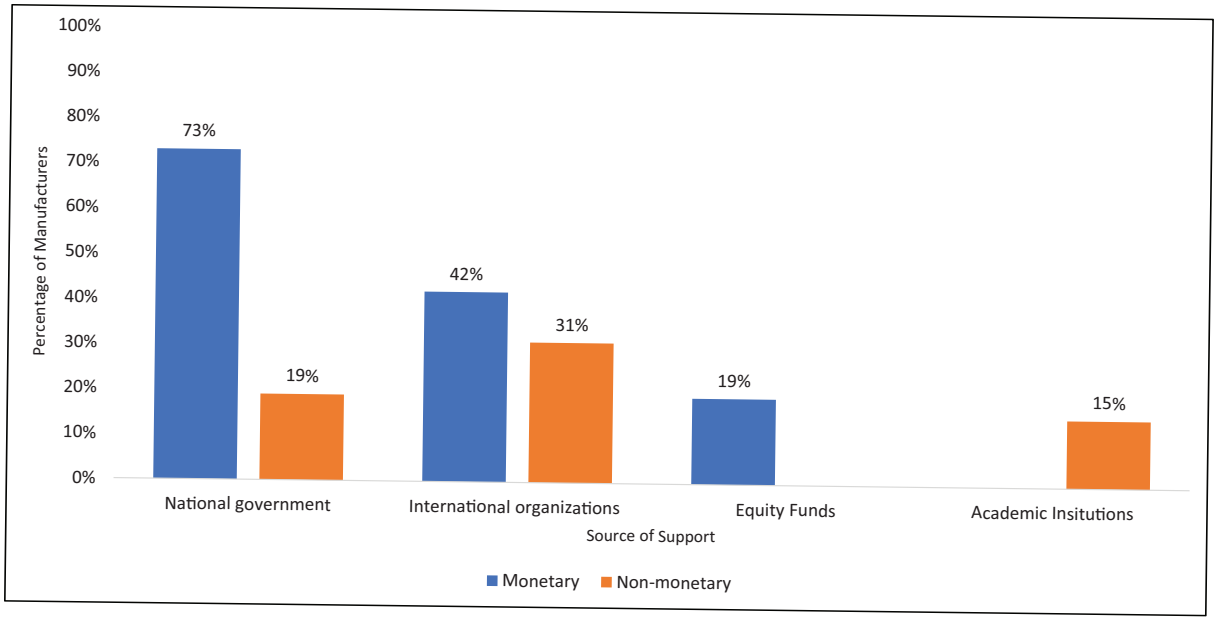

Fig. 6A. Monetary and non-monetary support received by manufacturers. Percentage of manufacturers that have received monetary or non-monetary support from a preselected list of organization types.

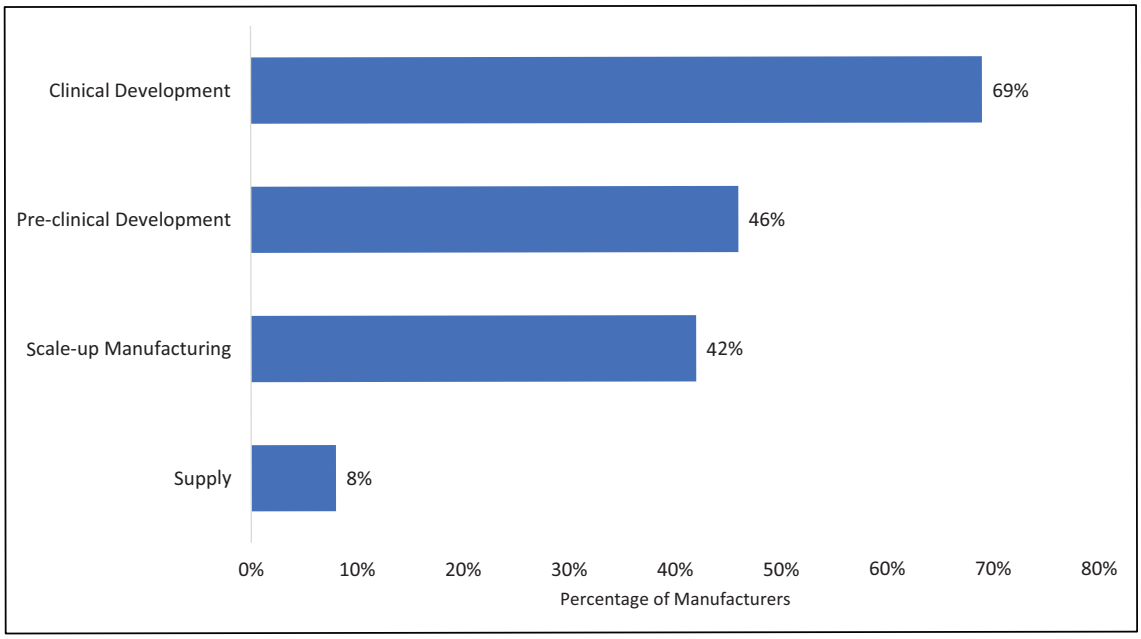

Fig. 6B. Manufacturing processes for which manufacturers have received funding support. Percentage of manufacturers that have received funding support for the predefined list of manufacturing processes.

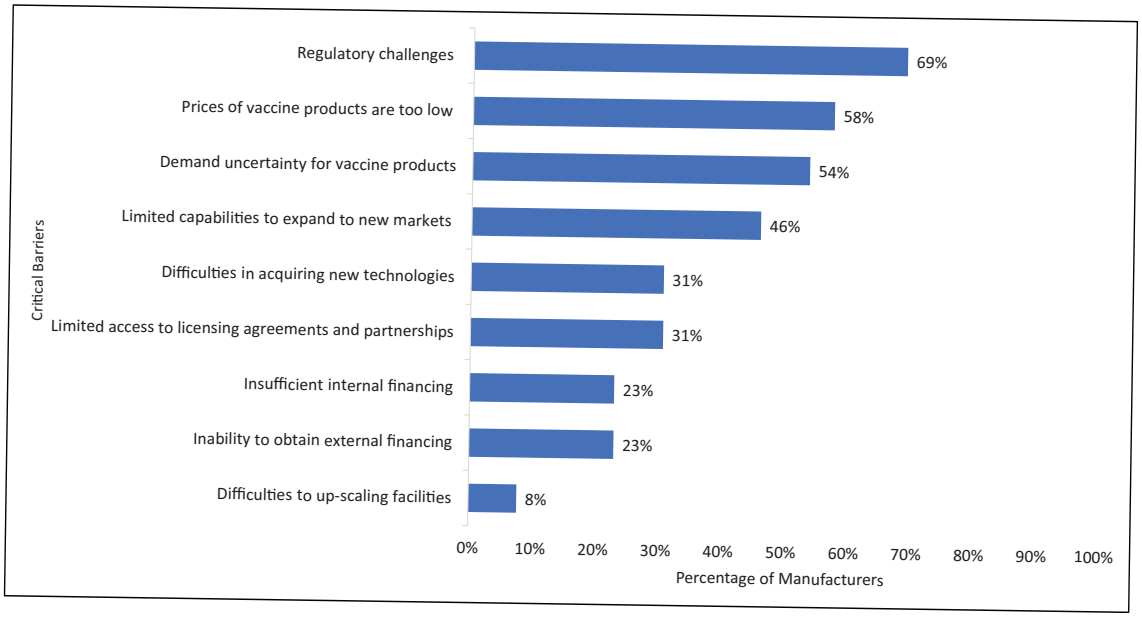

Fig. 7A. Critical barriers for vaccine manufacturers to sustainably manufacturer vaccines. Manufacturers were requested to select their top three critical barriers, from a preselected list of nine barriers, for their company to sustainably manufacturer vaccines.

and increase access to COVID-19 vaccines, particularly in LMICs. With a persistent need to increase vaccine production in developing countries, DCVMs will require continued support from governments, financing organizations and stakeholders to scale-up manufacturing capacities [23].

In the past decade, DCVMs have increasingly engaged in vaccine development, effectively developing vaccines to mitigate unmet health needs and improve programmatic ease of use and affordability in key disease areas [11]. Importantly, R&D efforts from DCVMs have made previously high-priced vaccines affordable in LMICs [29]. Furthermore, DCVMs are generally more receptive than large MNCs to develop vaccines against neglected diseases due to the lack of commercial viability for MNCs [29].

DCVMs efforts in advancing R&D portfolios balanced with second generation and novel vaccine candidates are key in refueling the industry's R&D ecosystem and contributing to the sustainable development of vaccines [30,31].

4.2. Large manufacturing capacities

A large capacity to produce vaccines resides in developing countries. It is reported that over 50% of the nearly 11 billion doses of

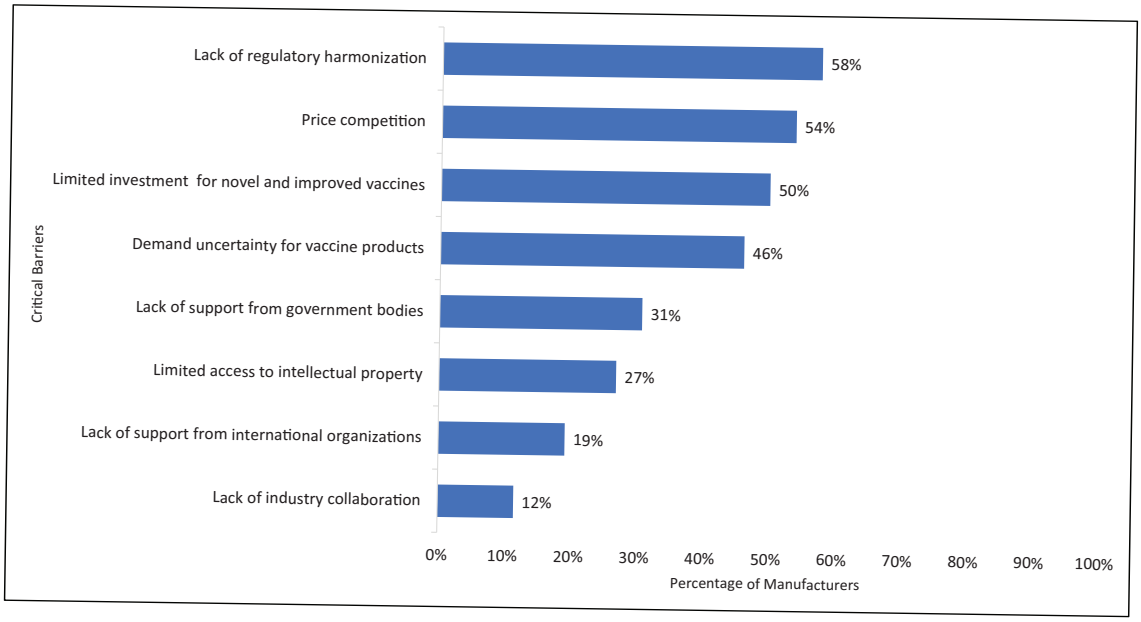

Fig. 7B. Critical barriers for the vaccine industry to ensure the sustainable supply of high-quality vaccines. Manufacturers were requested to selected their top three critical barriers, from a preselected list of eight barriers, for the vaccine industry to sustainably produce and supply vaccines globally.

COVID-19 vaccines were produced by DCVMs [32]. Most of this production capacity resides in the WPR and SEAR [18,33].

The large manufacturing capacities of DCVMN member companies are critical to global immunization efforts, particularly in LMICs, with DCVMN members contributing over 50% of the vaccine doses to Gavi markets [34]. DCVMs are capable of supplying vaccines to LMICs at affordable prices because high fixed costs are spread over a large volume of doses [13]. This business model has proven successful and viable when manufacturers supply large domestic markets and/or access international markets, often through the WHO PQ system [13].

During the COVID-19 pandemic there has been an urgent need to scale-up manufacturing capacity to satisfy the demand for COVID-19 vaccines. Existing facilities have expanded manufacturing capacity while numerous new entrants have developed vaccine manufacturing capacity. This has been crucial to the pandemic response but raises questions of over-capacity and the risk of idle facilities post-pandemic, which will be discussed later in this article.

4.3. Local and international vaccine supply

Historically, most DCVMs were state-owned and primarily mandated to manufacture vaccines domestically. However, in the last two decades several factors have contributed to an industry evolution that now sees a more balanced composition of private, publicly traded, and state-owned manufacturers [13].

DCVMs operate in many of the world's most populous countries therefore high volumes of doses are required to fulfill national demand. However, with industry progression, particularly in BRIC countries, DCVMs are increasingly positioned to sufficiently supply domestic markets. Consequently, new entrants and incumbents are inclined to access regional and international markets and prioritize the development of innovative vaccines to be competitive. These actions will further impact the global vaccine market, likely in the form of lower prices [35].

DCVMs global supply is critical to equitable access, notably DCVMs acquiring WHO PQ for their vaccine products enables them to supply vaccines globally through UN agencies. Pooled procurement by UN agencies involves long-term contracts which benefit the manufacturer by offering demand certainty and health systems by facilitating a consistent supply of affordable vaccines. For example, DCVM entry into high-value product categories has induced price competition, increasing vaccine affordability and supply security in GAVI markets for pentavalent, rotavirus and PCV vaccines [14,36].

4.4. Partnerships to increase vaccine development and access

Partnerships for vaccine production increase global access to vaccines. During the COVID-19 pandemic there has been an unprecedented level of industry collaboration. Licensing agreements, such as those between AstraZeneca and the Serum Institute of India and Bio-Manguinhos/Fiocruz of Brazil, and Johnson & Johnson's agreements with Biological E of India and Aspen in South Africa are crucial in increasing COVID-19 vaccine access in LMICs [37]. The willingness and urgency to actively form partnerships during the COVID-19 pandemic should be sustained post-pandemic to address more global health challenges, such as immunization gaps between LMICs and HICs in key disease areas.

Partnerships are equally critical to developing novel and improved vaccines. The proliferation of public and private entities driving the discovery and early development stages of vaccine development has drawn attention to the challenge of late-stage development, the most expensive and labor-intensive part of vaccine development [38]. One strategy that alleviates this impediment involves biotechnology companies, MNCs, research institutions, and agencies such as CEPI and the International Vaccine Institute (IVI) driving early-stage development to proof of concept before entering licensing agreements with companies with the manufacturing capabilities, capacities, and incentives to advance late-stage development and commercialize the product [30,38].

This multistakeholder approach to vaccine development is particularly important for developing vaccines that lack strong commercial cases e.g., poverty-related, and neglected diseases (PRND). Product development partnerships (PDPs) are Public-Private Partnerships (PPPs) that serve to develop technologies

and products for populations underserved by market forces [39]. A key example is the Serum Institute of India partnering with WHO, PATH and the Gates Foundation, among others to develop and produce at scale a meningitis vaccine for Africa (MenAfriVac) at a low price, with the objective of eliminating epidemic meningitis in Africa [38]. Another recent example is the Cholera Vaccine Program launched by the IVI, which resulted in EuBiologics of South Korea engaging in technology transfer and a PDP to develop and produce a safe and effective oral cholera vaccine. The vaccine received WHO PQ, increasing the supply of cholera vaccines globally [40]. DCVMs engagement in PDPs is a mechanism to facilitate development of vaccines for PRNDs and reduce the burden of infectious disease in LMICs [21,29]. For example, MenAfriVac almost eliminated the incidence of the disease in countries participating in the vaccination campaign [41]. Additionally, PDPs facilitate technology acquisition, the transfer of know-how and best practices, and access to funding - three forms of support which DCVMs report as critical to expanding their manufacturing capabilities [23,39].

Importantly, strong technological capabilities, historical performance, and reputation of DCVMs are all key factors that enable DCVMs to engage in partnerships with MNCs, research institutions, and international organizations [13].

4.5. External support for improved vaccine manufacturing and health security

External investments in pre-clinical and clinical development of COVID-19 vaccine candidates have played a major role in companies' ability to develop vaccines in record time [42]. Furthermore, governments in both developing and developed countries have invested in expanding domestic manufacturing capacities to increase local production and health security. It is important that the urgency and significant commitments of stakeholders during the COVID-19 pandemic are carried over to existing disease areas where there are unmet global health needs e.g., for tuberculosis, malaria.

In addition to upfront investments, non-monetary support helps manufacturers develop the know-how and skills to sustainably manufacture vaccines [43]. A recent study among DCVMs identified that in adopting and utilizing vaccine technologies, training coupled with funding is a strong need [23]. To support DCVMs sustainably develop and produce vaccines training programs should focus on emerging technologies such as approaches to mRNA platforms, automation, and artificial intelligence to facilitate the development of capabilities and best practices that more closely mirror those of manufacturers in developed countries.

4.6. The aspirational plans of DCVMs

The COVID-19 pandemic has accelerated a paradigm shift in the vaccine industry. The effectiveness and potential of new manufacturing technologies, the need for local production for health security, and the increased value of global vaccine markets, among other factors are reshaping the industry [6,44]. DCVMs intentions to increase production capacity and access new markets should increase vaccine availability globally. Furthermore, the advantages of DCVMs engaging in the development novel and improved vaccines are twofold; firstly, licensure of novel and improved vaccines can help reduce unmet burden of infectious diseases particularly in LMICs and secondly, these products provide manufacturers with a competitive advantage that is critical to their viability in a highly competitive industry.

4.7. Key considerations for sustainable vaccine development and production

4.7.1. Strengthening regional capabilities and pandemic preparedness

New entrants and the growth of incumbent vaccine manufacturers in all regions should positively impact timely and equitable access to vaccines during and between pandemic periods. A more geographical diverse industry landscape should improve affordability and supply security, however, lower prices, a likely result of increased competition threaten the viability of vaccine manufacturers. Low prices for vaccine products were the second-most cited barrier to sustainable manufacturing for DCVMs. Furthermore, lower prices can lessen the likelihood that manufacturers have sufficient internal financing to invest in vaccine R&D. This trade-off between the benefits of improved regional health security and the downstream consequences of market saturation is critical to all efforts in maximizing the public health benefits of vaccines.

This study identified that there may already exist underutilized capacity among DCVMs, particularly in the WPR and SEAR. The reported underutilized capacity may likely be a result of new facilities yet to be in operation. However, underutilized capacity, which could also be a result of supply–demand imbalances or poor market predictability, rises the opportunity cost of operating facilities for manufacturers. This can lead to facilities shutting down or being repurposed to produce other, often more profitable, pharmaceutical products. Better visibility on demand forecasting and capacity to enter long-term contracts and advance market commitments (AMCs) with governments and global procurement agencies will help alleviate the burden of demand uncertainty which inhibits manufacturer's ability to sustainably manufacture and supply vaccines.

South America and Africa are two regions in which expanded regional vaccine manufacturing capacities will greatly impact health security and pandemic preparedness. The DCVMs in South America operated at near capacity in 2021, however these facilities are much fewer in number and have lower average manufacturing capacity than those in the Asian regions. In Africa, the pandemic critically highlighted the need to expand the limited capacities and capabilities for vaccine manufacturing on the continent [17]. To improve vaccine manufacturing on both continents scaling up capacity of existing facilities and new entrants in the industry will be required. Specifically, any new facilities in these regions must consider product portfolios that optimally meet regional health needs and focus on establishing a market niche [44]. New entrants should aim to fill market gaps rather than directly competing with incumbents, increasing the diversity of capabilities in the region. A transparent, coordinated approach between new entrants, established manufacturers and regional governments will be required to ensure these efforts to improve regional health security are sustainable. Part of this effort can include regional governments securing markets for local manufacturers and established DCVMs providing know-how and forming regional partnerships with new entrants [44].

International organizations and NGOs, by supporting improvements in regional capabilities, greatly help regional health security but also global pandemic preparedness and response. An important initiative tying these together is CEPI's efforts in launching a global network of vaccine development and manufacturing facilities to rapidly respond to future epidemic and pandemic threats [45]. The globally distributed facilities would be supported by CEPI through workforce development, and the matchmaking of developers and manufacturers with the objective to enable rapid access to vaccines, particularly improving access in LMICs. CEPI will also work to keep facilities active, particularly between pandemics, critical to ensuring that facilities are sustainable.

4.7.2. Increasing market access and regulatory harmonization

Exporting vaccines increases manufacturers customer base and often, in the case of supplying vaccines to upper-middle and high-income countries, increases the price received for vaccine products. Exporting is critical to manufacturers in countries with an insufficient population size for domestic manufacturing to be viable and for manufacturers aspiring to compete internationally, yet it remains a challenging task.

Limited capabilities to expand to new markets was the fourth most cited critical barrier to DCVMs sustainability, and two key factors contributing to this limited capability: regulatory challenges and demand uncertainty, were the most and third most cited critical barriers to sustainable manufacturing.

Greater harmonization of global regulatory agencies and advancements in regulatory science would shorten vaccine development timelines and partially alleviate the barriers to achieving licensure and entering new markets for vaccine manufacturers [7,46,47]. This was observed during the COVID-19 pandemic as regulatory flexibilities and close collaboration between key stakeholders during vaccine development helped vaccines get approved for use in less than 12 months [47]. To reap the public health benefit of these novel regulatory approaches and the lessons learned during the pandemic, specific interventions in LMICs should be considered. Notably, there is a need to increase regulatory capacity – both at the level of national or regional regulatory agencies and for vaccine manufacturers. Expanding regulatory infrastructure will increase the efficiency of regulatory processes, expediating approval timelines for DCVMs [47]. Regional harmonization of regulatory standards would be a key step in improving regional health security by enabling established regional manufacturers to supply of vaccines throughout the region. This would both increase timely access to vaccines but also reduce the costs and time associated with obtaining approvals in each target country for the DCVM, incentivizing their vaccine manufacturing investments. Additionally, investments in workforce development to improve understanding of country approval procedures and WHO PQ requirements can increase the number of manufacturers exporting vaccines bilaterally or to UN agencies, facilitating global access to vaccines.

Improving data access and demand forecasting will enhance DCVMs capabilities in entering new markets. This is particularly important in accessing markets that self-procure vaccines, such as non-Gavi eligible MICs. The availability of data and market intelligence can help DCVMs seek commercial opportunities and inform their strategic decision-making.

4.7.3. Partnerships for late-stage vaccine development

Novel vaccine technologies and process innovations can reduce the time and costs of vaccine development [48,49]. Increased efficiency in vaccine development may incentivize vaccine developers to increase R&D activity, potentially refueling global R&D pipelines. Nevertheless, in several vaccine categories, particularly those needed in LMICs, investments in vaccine development may remain suboptimal. Vaccines to be used in LMICs, given the incentive structure, are rarely developed alone. Rather, private and public efforts contribute at different stages of vaccine development [31]. In the absence of market incentives for MNCs, the development of vaccines for developing countries must be led by DCVMs in partnership with private and public sector actors. Rappuoli et al. (2019) suggest that a sustainable model for vaccine development could see DCVMs receive technology transfers from MNCs to advance candidates through late-stage development and commercialization. This would permit both parties to make a sustainable return [38]. The lack of partners available to be technology recipients and commercialization partners has been reported as a key challenge to the vaccine ecosystem [7]. However, here we have identified that a subset of DCVMs have both the capabilities and aspirational plans to acquire technology transfers and develop novel and/or improved vaccines. Therefore, stakeholder efforts should focus on facilitating these partnerships, aligning the incentives and technical capabilities of developers and manufacturers to bring more vaccines to market. Advancing late-stage development of vaccine candidates through industry partnerships and PDPs is an important void in the global ecosystem which several established DCVMs can fill.

4.8. Research limitations

The research design used an online survey hence this may have resulted in measurement errors inherent of such survey processes. To minimize the likelihood of measurement errors that may risk biasing the study results, questions were principally close-ended and any questions that required numeric entry clearly specified the units of measurement. Furthermore, responding manufacturers may have overstated their capabilities or capacities potentially impacting the overall study findings. However, given all respondents were made aware that responses would be anonymized and aggregated the likelihood that manufacturers purposefully aggrandized is low.

All DCVMN member companies were invited to complete the survey. As 16 companies, did not submit responses, a bias may threaten the overall validity of the findings. However, we posit that a response rate of approximately 62% was sufficient of a correlate representation to address the core issues scoped in the aims of the paper. If a bias is present, it would likely be an underestimation of the reported average R&D and product portfolio size, and production capacity as several of the largest DCVMs, from the South-East Asia and Western Pacific regions, did not participate in the survey.[5]

To better quantify the sustainable vaccine manufacturing ecosystem in developing countries, future studies should endeavor to collect both quantitative and qualitative insights from a wider range of vaccine manufacturers but also from local governments and stakeholders that have an equally important role in ensuring sustainable manufacturing in developing countries. Additionally, to minimize any effect of response bias or measurement error, data collection would be improved by collecting data onsite in person.

5. Conclusion

Sustainable vaccine manufacturing is critical to protecting all people against known and emerging infectious diseases. People in LMICs are subject to the highest health economic burden of infectious diseases; hence ensuring the timely and equitable access of vaccines to these populations is of critical importance in global public health. DCVMs are fundamental in providing high-quality, affordable vaccines in these low-resource settings. These organizations are actively working to expand their technical capabilities, manufacturing capacities, and global outreach to increasingly contribute to a healthy vaccine industry. The role of these manufacturers, and the stakeholders that help enable them, will be pivotal in ensuring global access to vaccines and improved pandemic preparedness in the future.

6. Disclaimer

The authors alone are responsible for the statements and expressed in this article, which do not necessarily represent the

[5] To provide a complete list of DCVMN members that responded to the survey (and those that did not) may not be ethical as it would result in the disclosure of confidential information as per terms of the survey. The geographical location of non-respondents is detailed in Figure 1a.

views, decisions or policies of any mentioned institutions mentioned in this report, or with which the authors are affiliated.

Data availability

The data that has been used is confidential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.10.044.

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