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Developing-country vaccine manufacturers' technical capabilities can make a difference in global immunization

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ABSTRACT

Members of the Developing Countries Vaccine Manufacturers' Network (DCVMN) have been actively engaged in the development of COVID-19 vaccine candidates. According to the WHO COVID-19 vaccine landscape updated on 29 December 2020, 18 member manufacturers had vaccines in preclinical or clinical trials, including three members with candidates in Phase III trials. Once successful candidates have been identified there will be a need for large scale vaccine manufacturing and supply, in which DCVMN member manufacturers can play a key role. In an internal survey in 2019, DCVMN members reported the capability to supply over 3.5 billion vaccine doses annually, and the provision of over 50 distinct vaccines to 170 countries. To describe the capabilities of DCVMN member manufacturers more precisely, a 121-question survey was circulated to 41 Network members. The survey assessed the manufacturers' capabilities in utilizing various technology platforms, cell cultures and filling technologies, in addition to their capacities for manufacturing drug products. The survey also evaluated manufacturers' preparedness to dedicate existing capacities to COVID-19 vaccine production. Results revealed that sampled manufacturers have strong capabilities for manufacturing vaccines based on recombinant technologies, particularly with mammalian cells, and microbial and yeast expression systems. Capabilities in utilizing cell cultures were distributed across multiple cell types, however manufacturing capacities with Vero and CHO cells were prominent. Formulating and filling findings illustrated further large-scale capabilities of Network members. Sampled manufacturers reported that over 50% of their capacity for vaccine manufacturing could be dedicated to COVID-19 vaccine production.

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1. Introduction

On March 11th 2020, the World Health Organisation (WHO) declared the COVID-19 disease a pandemic [1]. At the end of 2020, over 85 million cases of COVID-19 had been diagnosed and over 1.8 million people had died [2]. The pandemic has led to a rapid international public health response to manage the spread of disease, with many nations imposing social distancing or lockdown, wearing of masks and travel restrictions [3]. The impact on the global economy and on social well-being has been significant [4]. Global leaders and experts have been tasked with finding an optimal balance between managing the health impact of COVID-19 and the economic and social implications.

Scientists have cautioned that a COVID-19 vaccine may not be a 'silver bullet' to end the pandemic [5,6], yet, historically, vaccination has been one of the most successful interventions in health

[7]. On January 10th 2020, the genetic sequence of the coronavirus that causes COVID-19 was published [8], initiating the global race to develop a vaccine [9]. The first COVID-19 vaccine candidate entered clinical trials on March 16th 2020 [10]. An unprecedented level of vaccine development is taking place. The December 29th update of the 2020 WHO landscape of vaccine candidates listed 60 COVID-19 vaccine candidates in clinical evaluation and another 172 candidates in pre-clinical evaluation [11]. Across the 60 candidates in clinical trials eight unique vaccine technology platforms are utilized, including both traditional technologies for inactivated and protein subunit vaccines and next-generation nucleic acid technologies [9]. Many different organisations are developing COVID-19 vaccine candidates: non-profit organisations, public institutes, academic institutes, multi-national corporations, biotechnology firms and manufacturers from developing countries [9]. This report focuses on manufacturers from developing countries who are members of the Developing Countries Vaccine Manufacturers' Network (DCVMN).

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The DCVMN is a public health-driven, international alliance of 41 vaccine manufacturers from 14 countries and territories engaged in vaccine research, development, manufacturing and supply for local and global use. DCVMN members have been actively engaged in COVID-19 vaccine development [12]. By the end of 2020, 9 DCVMN manufacturers had candidates in clinical trials, including three members with candidates in Phase III. An additional nine member manufacturers had candidates in pre-clinical evaluation [11]. Complementing these research and development successes, DCVMN member manufacturers have strengths in production of high-quality vaccines in large volumes. An internal DCVMN survey previously revealed that 37 member manufacturers had the capacity to supply over 3.5 billion vaccine doses annually [12]. This included multivalent vaccines and represents even higher capacity to make individual antigens [12]. Vaccines against 50 distinct diseases across almost 200 products were supplied to over 170 countries [13]. Furthermore, 13 member manufacturers had vaccine products pre-qualified by WHO, making those products eligible for procurement by UN agencies.

The COVID-19 pandemic has generated unprecedented public health collaboration between multiple stakeholders. A key example is the COVAX facility. Led by Gavi, CEPI and WHO, it is “a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines” [14]. This instrumental global collaboration aims to accelerate the development and production of COVID-19 vaccines with the goal of delivering two billion doses of safe, effective vaccines by the end of 2021 to control the acute phase of the pandemic [14]. Furthermore, the need for accelerated vaccine development and rapid production has seen an increase in partnerships between developers, manufacturers, and other key stakeholders, with organisations each leveraging their respective resources and capabilities [15].

This project aimed to identify specific capabilities and capacities of DCVMN member manufacturers and to assess how much of their existing capacity can potentially be dedicated to COVID-19 vaccine production. In publishing the joint capabilities of DCVMN manufacturers in a public domain, this study draws attention to the vital role such manufacturers can have in the production and distribution of COVID-19 vaccines to make a difference in the course of the pandemic. Funding from international stakeholders and partnerships between vaccine developers and manufacturers will be critical for accelerating supply of COVID-19 vaccines.

2. Method

To quantify the manufacturing capabilities of DCVMN members, a 121-question survey (Annex 1) was circulated to 41 Network manufacturers. Objective questions were used to ascertain both capabilities and capacities and estimate how much of current capacity could be dedicated to COVID-19 vaccine production. The survey focused on four key segments: (1) technology platforms (2) cell cultures (3) drug product capacities and (4) filling technologies. For each of these, manufacturers were asked whether they used a specific technology or platform. For each one used, they were asked to share production volume, total number of manufacturing lines (and the number of which could be dedicated to COVID-19 vaccine production), and also the percentage of capacity that could be dedicated to COVID-19 vaccine production.

2.1. Technology platforms

Six specific technology platforms were considered: purified plasmid DNA, purified RNA by in-vitro transcription, lipid nanoparticle formulations of mRNA, vaccines based on recombinant tech-

nologies using mammalian cells (e.g., Vero, Chinese Hamster Ovary (CHO) cells), vaccines based on recombinant technologies using non-mammalian cells (e.g., insect cells, Primary Chick Embryo Cells (PCEC)), and vaccines based on microbial or yeast expression systems (e.g., *Escherichia coli*, *Pichia pastoris*). In analysing the results, the data points for purified RNA by in-vitro transcription and lipid nanoparticle formulations of mRNA were merged into the category RNA vaccine technologies.

To understand future capabilities, manufacturers were asked to share all technology platforms which they are currently implementing or plan to implement in the next 5 years.

2.2. Cell culture

Capabilities related to ten specific cell cultures were considered: Vero, Chinese Hamster Ovary (CHO), Human Diploid, Baby Hamster Kidney (BHK), Human Embryonic Kidney (HEK-293), Madin-Darby Canine Kidney (MDCK), Primary Chick Embryo (PCEC), *Pichia pastoris*, *Saccharomyces cerevisiae* and *Escherichia coli*.

2.3. Drug product capacities

Total formulating capacity (L/day) was sought. Number of manufacturing lines was determined by how many manufacturing tanks were available for the following scales: 0-500L, 500-1000L, 1000-1500L, 1500-2000L, > 2000L.

Additionally, manufacturers were asked to identify which adjuvants they currently utilize.

2.4. Filling technologies

The survey focused on five specific filling technologies: glass vials, plastic tubes¹, blow-fill-seal (BFS), pre-filled syringes (PFS), and ampoules. Filling technologies were assessed by filled units per minute.

The survey was designed to be anonymous, however in a final segment, respondents were invited to share which organisation they represent and in which country their organisation is primarily based. Both questions were optional.

The survey was designed by Mr. Sai Prasad and Mr. Apoorv Kumar of Bharat Biotech International, in consultation with the DCVMN Secretariat. After the survey was drafted, the circulation, collection of data and analysis was completed by the DCVMN Secretariat. All 41 Network members were invited by the DCVMN Secretariat, by email, to complete the online survey. The final response was received on October 15th 2020. Overall, 26 member manufacturers responded to the survey resulting in a response rate of just over 63%. Two additional manufacturers stated that they could not complete the survey due to legal restrictions. The data was then analysed to produce the findings of this report.

3. Results

Data was aggregated based on the WHO Regions, grouped as WHO Western Pacific (11 manufacturers), WHO South-East Asia (9 manufacturers), WHO Americas (3 manufacturers) and WHO Other (3 manufacturers)².

3.1. Technology platforms

Among the sampled DCVMN members, recombinant technologies using mammalian cells were the most utilized platform with

¹ Plastic tubes are often referred to as plastic vials.

² WHO Other = WHO Africa, WHO Europe, and WHO Eastern Mediterranean

Table 1

Number of sampled DCVMN member manufacturers utilizing each vaccine manufacturing technology. Manufacturing technologies are divided into three categories: technology platforms, cell cultures, filling technologies.

Assessed manufacturing capabilities	Number of manufacturers using technology
Technology Platforms	
Recombinant Technologies using mammalian cells	14
Microbial or Yeast Expression Systems	11
Recombinant Technologies using non-mammalian cells	7
RNA Vaccine Technologies	2
Purified Plasmid DNA	1
Cell Cultures	
Vero	14
CHO	8
<i>E. coli</i>	8
HEK-293	5
<i>P. pastoris</i>	4
Human Diploid	3
MDCK	2
Primary chick embryo	2
BHK	1
<i>S. cerevisiae</i>	1
Filling Technologies	
Glass Vials	23
Pre-filled syringe	14
Ampoules	9
Plastic Tubes	2
Blow-fill-seal	1

14 members having manufacturing capabilities with this technology (Table 1). The next most frequently used technologies were microbial and yeast expression systems that were employed by 11 manufacturers, followed by recombinant technologies using non-mammalian cells (7 manufacturers). Less common were nucleic acid technology platforms. Only two manufacturers utilize RNA vaccine technologies, and one manufacturer utilizes purified plasmid DNA (Table 1).

The largest production volume was for recombinant technologies using mammalian cells, with a present capacity of 22,505 Litres, approximately 65% of which is based in the WHO Western Pacific Region (Fig. 1A). The Western Pacific Region also has strong manufacturing capacity using microbial or yeast expression systems, with 57% of the total production volume of 10,370 Litres manufactured in this region. Sampled manufacturers from the WHO South-East Asia Region were responsible for almost 59% of the production volume of vaccines based on recombinant technologies using non-mammalian cells (Fig. 1A).

The sampled manufacturers are prepared to dedicate considerable capacity to the production of COVID-19 vaccine candidates. The sampled manufacturers produced vaccines based on recombinant expression systems using mammalian cells on 24 manufacturing lines, of which 15 could be dedicated to COVID-19 vaccine production (62.5%). For microbial or yeast expression systems, 9 of 27 (33.3%) manufacturing lines could be dedicated, while 9 out of 10 (90%) of manufacturing lines used to produce vaccines based on recombinant technologies using non-mammalian cells could be available for COVID-19 vaccine manufacturing (Fig. 1B). Only one manufacturing line was reported in this survey for each of RNA vaccine technologies³ and purified plasmid DNA platforms, but both could be dedicated to COVID-19 vaccine manufacturing. Overall, approximately 53.4% of manufacturing lines utilized by the sampled manufacturers could be dedicated to COVID-19 vaccine production.

³ Two manufacturers indicated they utilized RNA vaccine technology; however, one manufacturer did not share information specific to manufacturing lines.

This study also explored future capabilities of DCVMN member manufacturers. Results showed that manufacturers are implementing modern technology platforms. More than any other technology, manufacturers are implementing purified plasmid DNA and RNA vaccine technologies (Fig. 1C).

3.2. Cell cultures

Vero cells were reported as the most widely utilized cell culture with 14 of the sampled manufacturers currently using this technology (Table 1). Another mammalian cell line, Chinese Hamster Ovary (CHO) cells and the bacterium *Escherichia coli* (*E. coli*) were the next most common, used by eight manufacturers each. Five manufacturers indicated they utilize Human Embryonic Kidney (HEK-293) and four utilized *Pichia pastoris* (*P. pastoris*) cells.

To further quantify manufacturers' capabilities, the total bioreactor volume (in litres) for each cell culture technology was sought (Fig. 2A). Together, the 26 sampled manufacturers have a bioreactor volume of over 18,000 L for CHO cells, with approximately 81% of this capacity coming from the WHO Western Pacific Region. The next largest capacity was for Vero cells, with over 11,000 L, followed by HEK-293 cells, for which the aggregate bioreactor volume was 10,105 L and is predominantly based in the WHO Americas and Western Pacific Regions (each region responsible for ~ 40% of the total volume).

As for technology platforms, the sampled manufacturers reported being prepared to dedicate a substantial amount of their cell culture manufacturing capabilities to COVID-19 vaccine production. Of the 20 manufacturing lines that use Vero cells, twelve could be dedicated to COVID-19 vaccine manufacturing (60%), while of the ten manufacturing lines using CHO cells, seven can be allocated to COVID-19 vaccines (70%). Furthermore, all of the sampled manufacturers' capacity to produce vaccines using HEK-293 cells and over 85% of the *E. coli* manufacturing lines could be dedicated (Fig. 2B). Overall, the sampled manufacturers reported having 59 manufacturing lines equating to almost 50,000 L of bioreactor volume. Approximately 61% of the manufacturing lines could be dedicated to COVID-19 vaccine production.

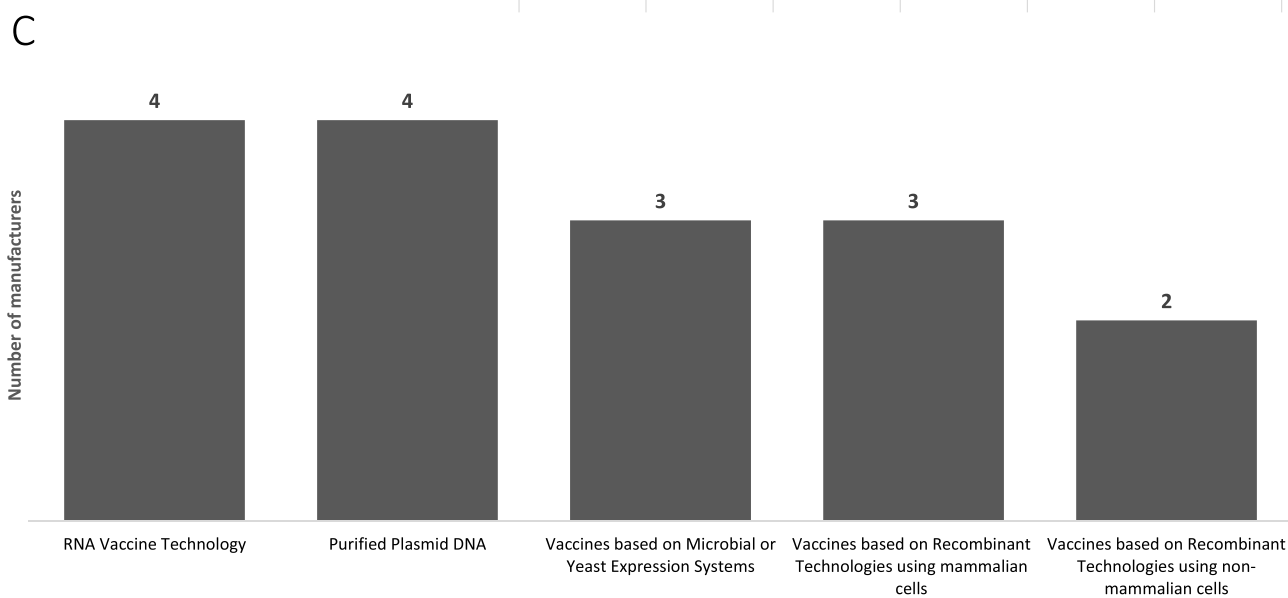
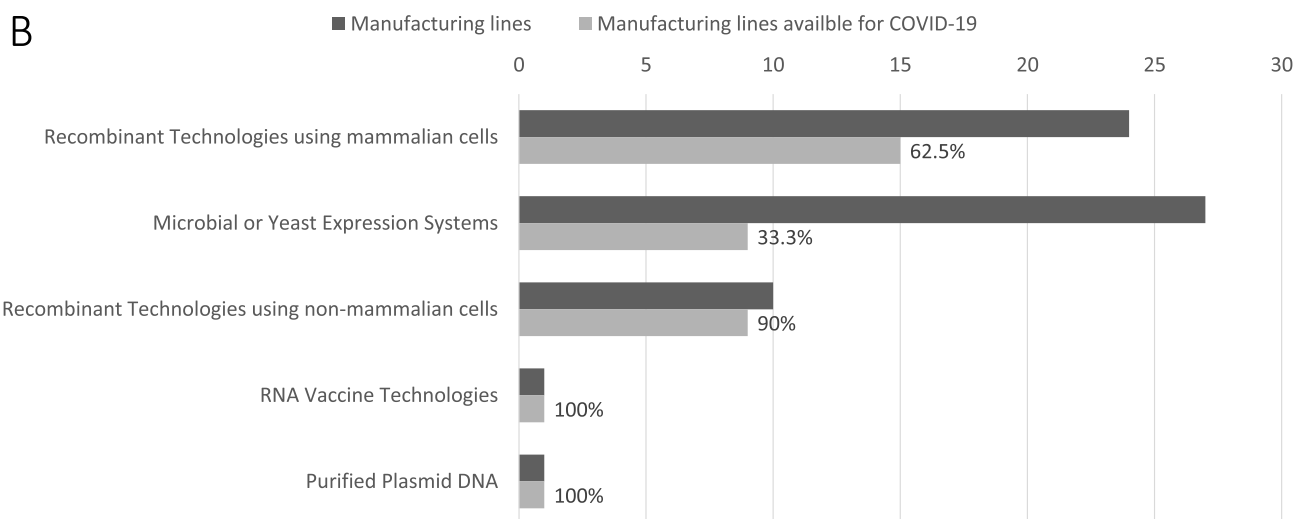
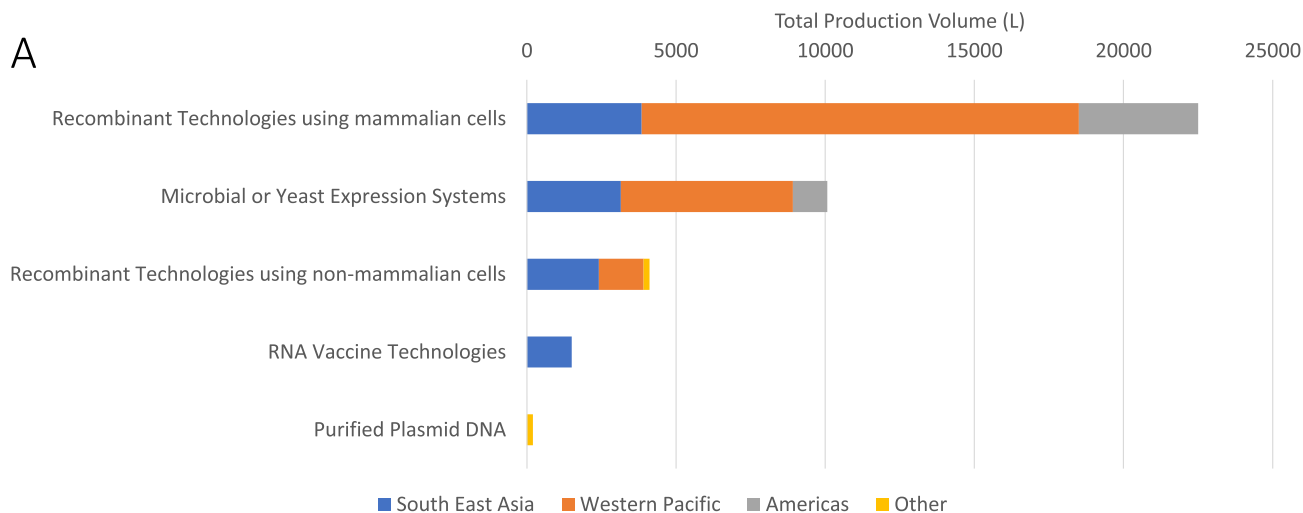
3.3. Drug product capabilities

In total, the sampled manufacturers reported having the capacity to formulate almost 18,000 L per day with approximately 48% of these capacities based in the WHO Western Pacific (Fig. 3A). The total formulating capacity was distributed across 109 manufacturing tanks which varied in size from 50 to 2000 L. A more in-depth analysis of the available formulating tanks is shown on Fig. 3B. In aggregate, approximately 50% of these manufacturing tanks could be dedicated to COVID-19 vaccine production.

On use of adjuvants, 19 of the sampled manufacturers used Alum while 3 formulated with MF59. Other adjuvants such as AS03, AS03B, 002C and CpG 1018 were each only used by one manufacturer.

3.4. Filling capabilities

Results indicate that sampled manufacturers have strong filling capabilities. Glass vials were the most utilized container, used by 23 manufacturers, followed by pre-filled syringes (14 manufacturers) and ampoules (9 manufacturers). Two manufacturers used plastic tubes while blow-fill-seal technology was only utilized by one manufacturer (Table 1).



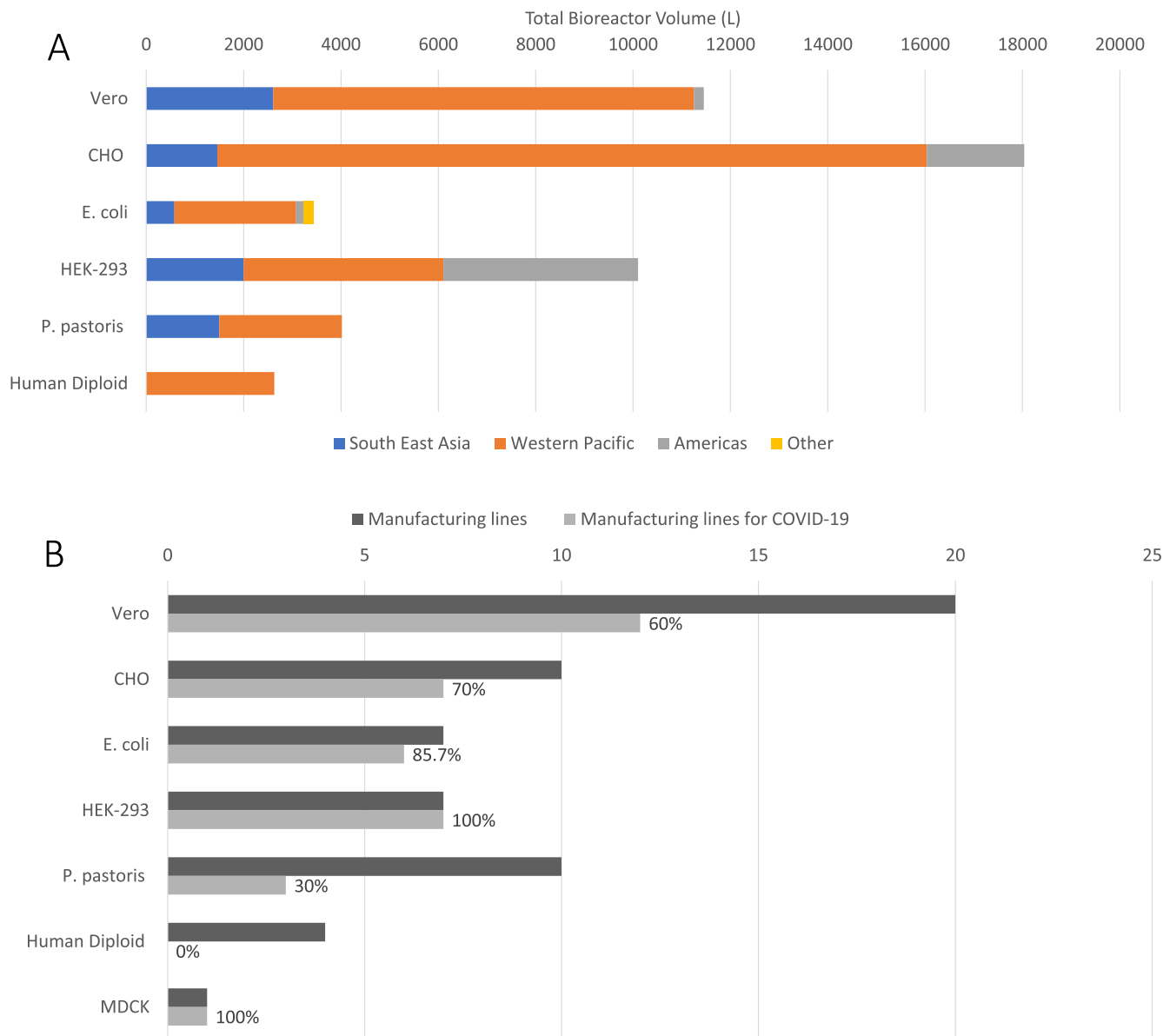


Fig. 2. A. Total bioreactor volume (measured in Litres) for each of the specified cell cultures. Bioreactor volumes were quantified in each WHO region. Note: not all manufacturers who indicated they utilize the cell culture shared their specific bioreactor volume, and in some cases shared data in different units. Any responses to this question that were not in correct units were omitted from the final output. **Fig. 2B. Total number of manufacturing lines and the percentage of which could be dedicated to COVID-19 vaccine manufacturing.** Across all cell cultures sampled manufacturers have 59 manufacturing lines of which 36 can presently be dedicated to COVID-19 vaccines (61%). Note: two manufacturers indicated that their manufacturing lines would be dedicated to COVID-19 vaccine production based on market requirements. The final output includes these as being available for COVID-19 vaccine production.

Fig. 1. A. Total production volume (measured in Litres) for each of the specified vaccine technology platforms. Production volumes were quantified in each WHO region. Note: not all manufacturers who indicated they utilize the platform technology shared their specific production volume, and in some cases shared data in different units. Any responses to this question that were not in correct units were omitted from the final output. The breakdown of the omitted data for each platform technology is: RNA Vaccine Technologies: one manufacturer indicated a production volume of 50–100 million doses. Recombinant technologies using mammalian cells: two manufacturers did not share total production volumes, one manufacturer indicated that T-flasks and a cell factory were used in their production process. Microbial or Yeast expression systems: one manufacturer did not indicate total production volume. In instances in which total production volume was provided as a range e.g. 1000–1500 Litres, the lower value was always used in the final output. **Fig. 1B. Total number of manufacturing lines and the percentage of which could be dedicated to COVID-19 vaccine manufacturing.** Across all platform technologies sampled manufacturers have 63 manufacturing lines of which 35 can presently be dedicated to COVID-19 vaccines (55.6%). Note: two manufacturers indicated that their manufacturing lines would be dedicated to COVID-19 vaccine production based on market requirements. The final output includes these as being available for COVID-19 vaccine production. **Fig. 1C. Number of sampled DCVMN members current implementing or planning to implement the technology platform in the next 5 years.** There was also the option 'other' for which one manufacturing indicated pneumococcal conjugate vaccines (PCV).

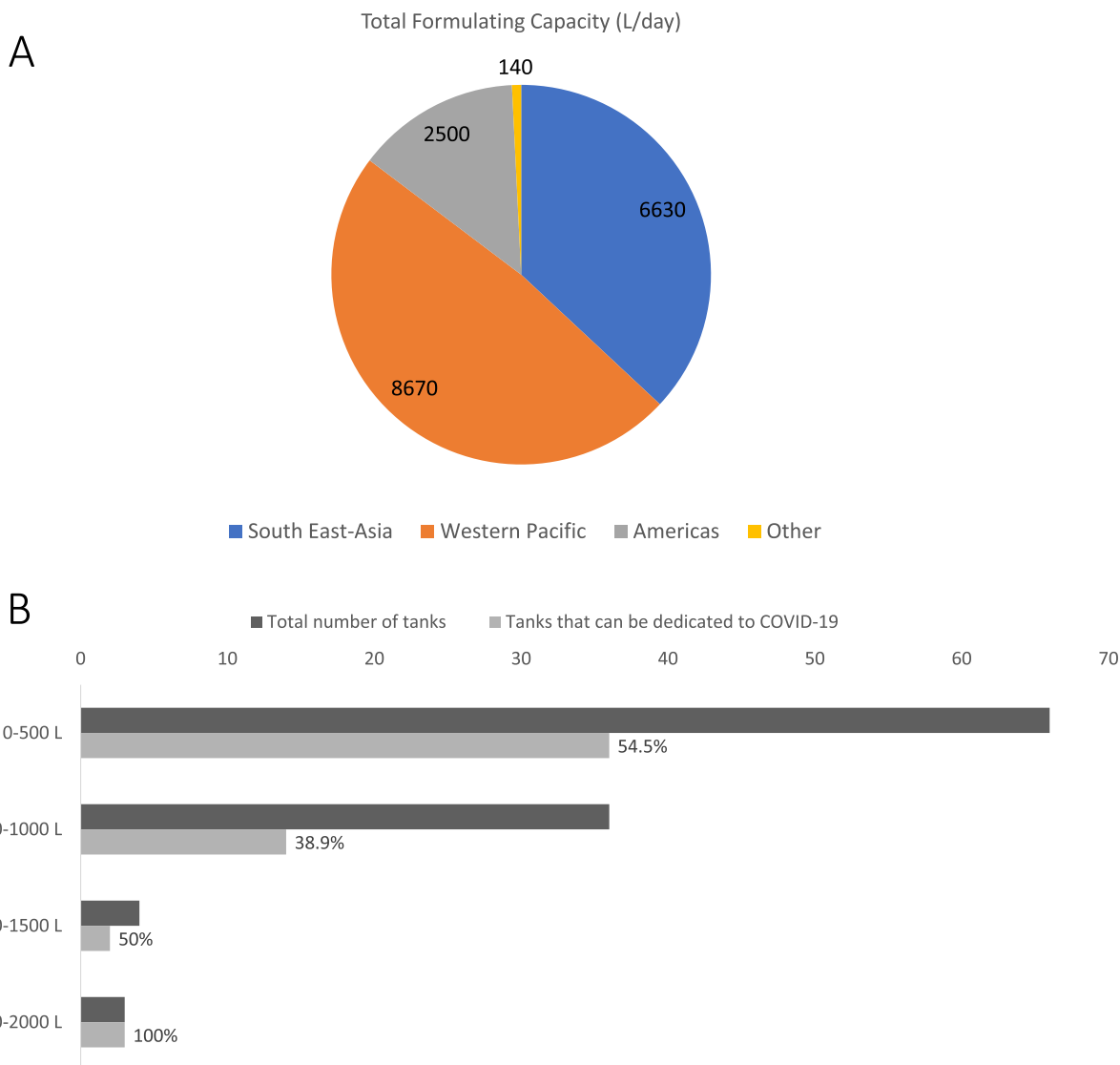


Fig. 3. A. Geographical breakdown of total formulating capacity measured in litres per day. 22 of the 26 sampled manufacturers indicated capabilities for vaccine formulation. Total formulating capacity of the 22 manufacturers was estimated to be between 17,940 – 18,795 L/day. For the output the lower estimate was used. Total formulating capacity was broken into WHO regions: Western Pacific (48%), South-East Asia (37%), Americas (14%), Other (1%). **Fig. 3B. Total number of formulating tanks and the percentage of which could be dedicated to COVID-19 vaccine manufacturing.** Sampled manufacturers have 109 formulating tanks of which 55 can presently be dedicated to COVID-19 vaccines (50%). Note: one manufacturer indicated that their formulating tanks would be dedicated to COVID-19 vaccine production based on market requirements. Final output includes these as being available for COVID-19 vaccine production.

Capabilities in using each filling technology were assessed by total filling capacity measured in filled units per minute⁴. Capabilities using glass vials was greatest, with the sampled manufacturers able to fill over 8600 per minute. Glass vials were followed by pre-filled syringes, at a capacity of 4000 vials per minute. For both filling technologies, approximately 73% of the current capacity resides in the WHO Western Pacific region. Sampled manufacturers have the capacity to fill over 2320 ampoules per minute (Fig. 4A).

Manufacturers are prepared to allocate a high percentage of their filling capacity to COVID-19 vaccine production. Glass vials were utilized across 51 manufacturing lines, and almost two-thirds could be dedicated to COVID-19 vaccines (62.7%). Results revealed manufacturing lines for pre-filled syringes and ampoules could also be dedicated at high rates (44.4% and 60% respectively). Further, plastic tubes, a filling technology for which, on aggregate, manufacturers can fill 405 tubes per minute, can be fully leveraged for COVID-19 vaccine production (Fig. 4B). Overall, 75 manufactur-

ing lines were listed across five key filling technologies, with 60% of capacity able to be dedicated to COVID-19 vaccine production.

4. Discussion

This study has quantified the capabilities DCVMN members across key areas of manufacturing, namely: technology platforms, cell cultures, formulation, and filling capabilities.

Vaccines are manufactured using a wide range of technology inputs, with the level of technological input and expertise required to produce safe and efficacious vaccines varying [16]. Results revealed the sampled manufacturers have significant capacity to produce vaccines based on recombinant technologies (particularly using mammalian cells). This is significant as 16 recombinant protein COVID-19 vaccine candidates are in clinical evaluation and as vaccines based on this technology have a strong history of triggering safe and robust immune responses in addition to being well suited for storage and transportation [17].

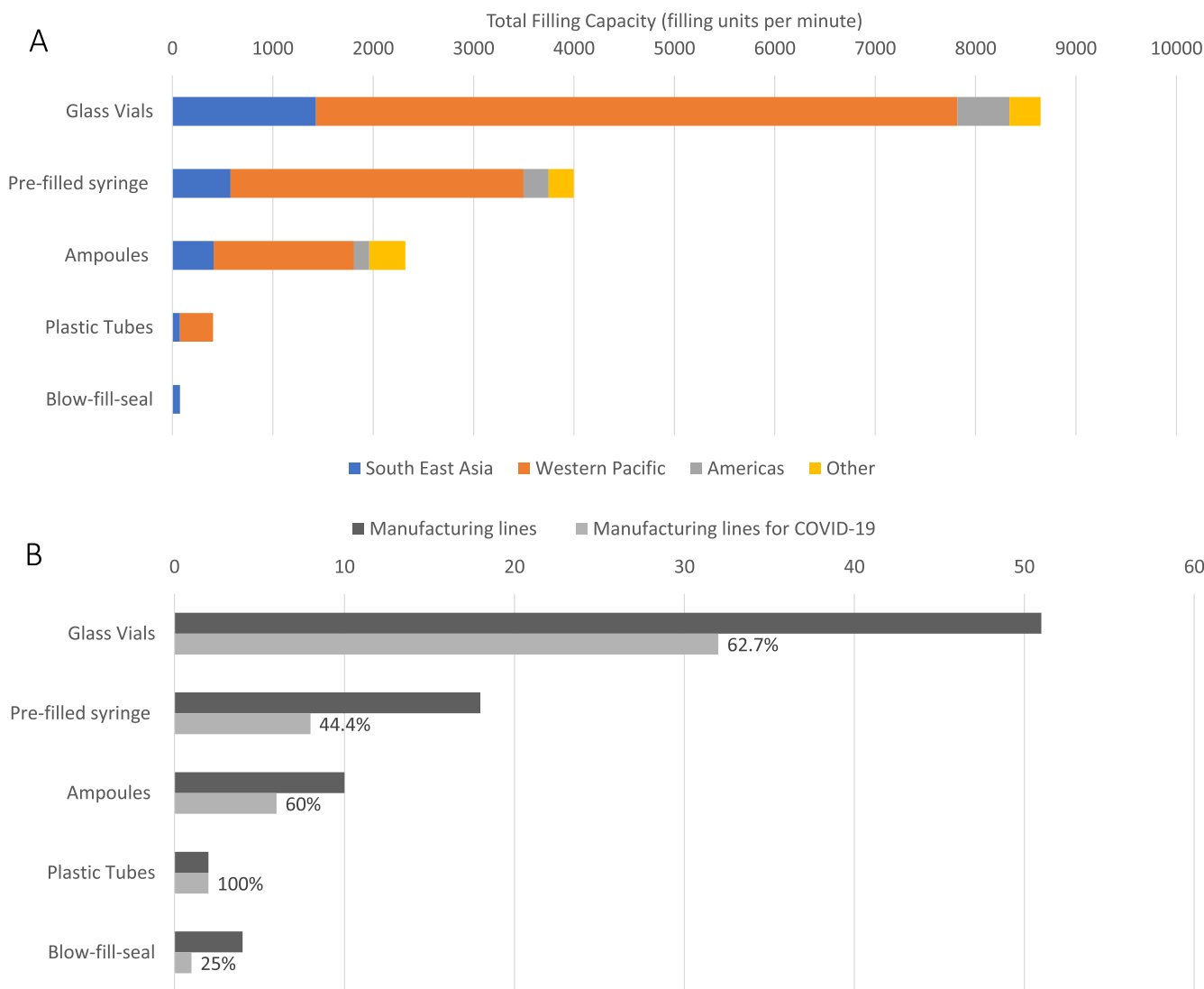


Fig. 4. A. Filling capacity (measured in tubes or vials per minute) for each of the specified filling technologies. Capacities were quantified in each WHO region. Note: not all manufacturers who indicated they utilize the filling technology shared their specific capacity. Any responses to this question that were not in correct units were omitted from the final output. The breakdown of the omitted data for each filling technology is: Glass vials: one manufacturer did not indicate filling capacity. In instances in which filling capacity was provided as a range e.g. 100–200 vials/minute, the lower value was always used in the final output. **Fig. 4B. Total number of manufacturing lines and the percentage of which could be dedicated to COVID-19 vaccine manufacturing.** Across all filling technologies sampled manufacturers have 85 manufacturing lines of which 49 could be dedicated to COVID-19 vaccines (57.6%). Note: four manufacturers indicated that their manufacturing lines would be dedicated to COVID-19 vaccine production based on market requirements. Final output includes these manufacturing lines as being available for COVID-19 vaccine production.

Furthermore, assessing DCVMN member manufacturers’ capabilities in development highlighted a motivation to implement nucleic acid-based technologies, a finding that is very relevant to the current COVID-19 vaccine landscape [11]. Nucleic acid vaccines can be rapidly adapted when a new virus emerges, as development can be based on sequence information alone, which has resulted in nucleic acid vaccines being the first COVID-19 vaccines to enter and, in the United States, to complete clinical trials [18,19,20]. The first two candidates to achieve authorization for use in the United States were vaccines based on lipid nanoparticle formulations of mRNA [19,20].

Capabilities in utilizing cell cultures were distributed across multiple cell types. Although manufacturing capacities with Vero and CHO cells dominated, sampled manufacturers indicated they also utilize HEK-293 cells in large volumes. These cells are widely used to propagate adenovirus vaccine vectors and produce high yields [21,22]. *P. pastoris* cell technologies which provide key benefits of rapid expression times and small culture volumes [23], are utilized by four sampled manufacturers.

Manufacturers have strong formulating capacities in three geographical regions which can support the global production of COVID-19 vaccines. Filling capabilities were illustrated across five main technologies, with glass vials leading both utilization and total capacity.

DCVMN member manufacturers’ capabilities and large manufacturing capacities are both significant assets for the production of COVID-19 vaccine candidates. Firstly, in terms of capabilities, the 60 candidates currently in clinical trials utilize eight different technology platforms [11] – each requiring different expertise and facilities [9]. With manufacturers having a broad range of capabilities they are positioned to scale up production of many of the candidates, particularly those based on recombinant protein technologies. Given the importance of rapid production and distribution of successful candidates, partnerships are already in place between developers and manufacturers, including those from developing countries. Key examples include AstraZeneca entering a licensing agreement with the Serum Institute of India to supply one billion doses of Oxford University’s non-replicating viral vector

COVID-19 vaccine candidate to low- and middle-income countries [24]. Biological E (India) has entered an agreement with Johnson & Johnson (J&J) to manufacture their COVID-19 vaccine candidate. The collaboration will involve J&J providing a technology transfer to Biological E to produce the vaccine [25]. The importance of collaboration in developing, manufacturing, and distributing COVID-19 vaccines is well illustrated by the collaboration between three DCVMN members: Sinovac of China, Instituto Butantan of Brazil, and PT BioFarma of Indonesia. Sinovac's inactivated COVID-19 vaccine candidate (Vero cell-based) is undergoing Phase III trials in both Brazil and Indonesia, conducted by Instituto Butantan and PT BioFarma, respectively. Furthermore, Sinovac will supply vaccine bulk to both organisations, allowing them to produce the vaccine locally. Brazil, China, and Indonesia account for approximately 24% of the world's population [26].

Secondly, large-scale manufacturing capacity will be required to gain immunization coverage globally. The COVAX facility aims to supply two billion doses by the end of 2021. This is to protect those who are most vulnerable, including frontline health care workers [14]. To protect all people from the impact of COVID-19, vaccines must be widely administered [27]. DCVMN member manufacturers are well positioned for global production and supply. These manufacturers are located in 14 countries and territories in which over 54% of the world's population reside. They currently supply vaccines to over 170 countries, have GMP- certified facilities and comply with international supply requirements [12]. The sampled manufacturers report that they can dedicate between 55 and 65% of their manufacturing capacity across technology platforms, cell cultures, formulation, and filling to COVID-19 vaccine production. Given that DCVMN members reported manufacturing capacity is over 3.5 billion doses annually, this represents a significant opportunity for making a difference in the production and supply of COVID-19 vaccines globally.

The capabilities and capacity of DCVMN manufacturers continue to be of paramount importance in supplying 'traditional' vaccines globally to ensure that ongoing requirements of national immunization programs are met [28].

5. Conclusion

The findings of this report indicate the role DCVMN member manufacturers can have in the global supply of COVID-19 vaccines. By the end of 2020, 9 DCVMN manufacturers had vaccine candidates in clinical trials. Beyond vaccine development, the existing capabilities of manufacturers will be crucial for the large-scale production and distribution of successful candidates. This report summarizes the capabilities of a sample of manufacturers across varying technology platforms, cell culture, formulation, and filling technologies. Results revealed both a diverse range of capabilities and a large production capacity. The manufacturers report that they are able to dedicate a large proportion of their manufacturing capacities to the production of COVID-19 vaccines. Transparent partnerships and collaborations for collective action will be essential to effectively and efficiently produce and supply vaccines globally. By quantifying the manufacturing capacities this report confirms that vaccine manufacturers from developing countries are well positioned to make a difference.

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.2021.07.044>.

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