



PROSUR

RAPID VACCINE SUPPLY DIAGNOSTIC FOR LATIN AMERICA AND CARIBBEAN REGION

Scaling up of Immunization Capacities in the PROSUR countries



Rapid Vaccine Supply Diagnostic for Latin America and Caribbean Region – Final Report

Scaling up of Immunization Capacities in the PROSUR countries

Immunization Subgroup

Health Group

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Acronyms

ASC	Available Supply for Commercialization
BCG	Bacillus Calmette-Guerin vaccine against tuberculosis
CELAC	Community of Latin American and Caribbean States
CEPAL	United Nations Economic Commission for Latin America and the Caribbean
CEPI	Coalition for Epidemic Preparedness Innovations
CMO	Contract Manufacturing Organization
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
DTP	Diphtheria Tetanus and Pertussis vaccine
DTP1	Diphtheria Tetanus and Pertussis vaccine first dose
DTP3	Diphtheria Tetanus and Pertussis vaccine third dose
EPI	Expanded Program on Immunization
HepB	Hepatitis B vaccine
Hib	Haemophilus influenzae type B vaccine
HIC	High Income Country
HPV	Human papillomavirus vaccine
IADB	Inter-American Development Bank
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
LAC	Latin America and Caribbean region
LMIC	Low- and Lower Middle-Income Countries
MCV1	Measles-Containing Vaccine first dose
MCV2	Measles-Containing Vaccine second dose
MI4A	Market Information for Access to Vaccines initiative
MMGH	MMGH Consulting
MMR	Measles, Mumps and Rubella vaccine
MMR-V	Measles, Mumps, Rubella and Varicella vaccine
MR	Measles-Rubella
mRNA	Messenger ribonucleic acid
NIP	National Immunization Program
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PCV	Pneumococcal Conjugate Vaccine
PCV1	Pneumococcal Conjugate Vaccine first dose
PROSUR	Forum for the Progress and Development of South America
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UMIC	Upper Middle-Income Country
UNDP	United Nations Development Program
UNICEF	United Nations Children's Fund
USD	United States Dollar
WGI	Worldwide Governance Indicators
WHO	World Health Organization
WUENIC	WHO/UNICEF estimates of national immunization coverage
YFV	Yellow Fever Vaccine

Executive Summary

The COVID-19 pandemic has highlighted the central role played by the timely and continued access to vaccines for minimizing mortality and morbidity impact of infectious diseases. Such central role is not limited to pandemic and epidemic events but extend to many endemic diseases for which vaccines exist. While at global level, supply of vaccines is generally sufficient to fulfil the ongoing demand from countries, several factors can affect access at regional and country level. Even under normal circumstances different epidemiological needs, specific policy decisions, country product preferences, registration constraints, procurement constraints can all lead individual countries or even regions to face access constraints irrespective of the global health of the market. During period of crisis additional factors enter into play, making access to vaccines more difficult: vaccine nationalism, interruption of supply chains, competition for access to input materials, pricing competition and product hoarding being some of the most prominent ones. An effective pandemic/outbreak preparedness strategy as well as a resilient routine immunization strategy must secure timely and uninterrupted access to vaccines.

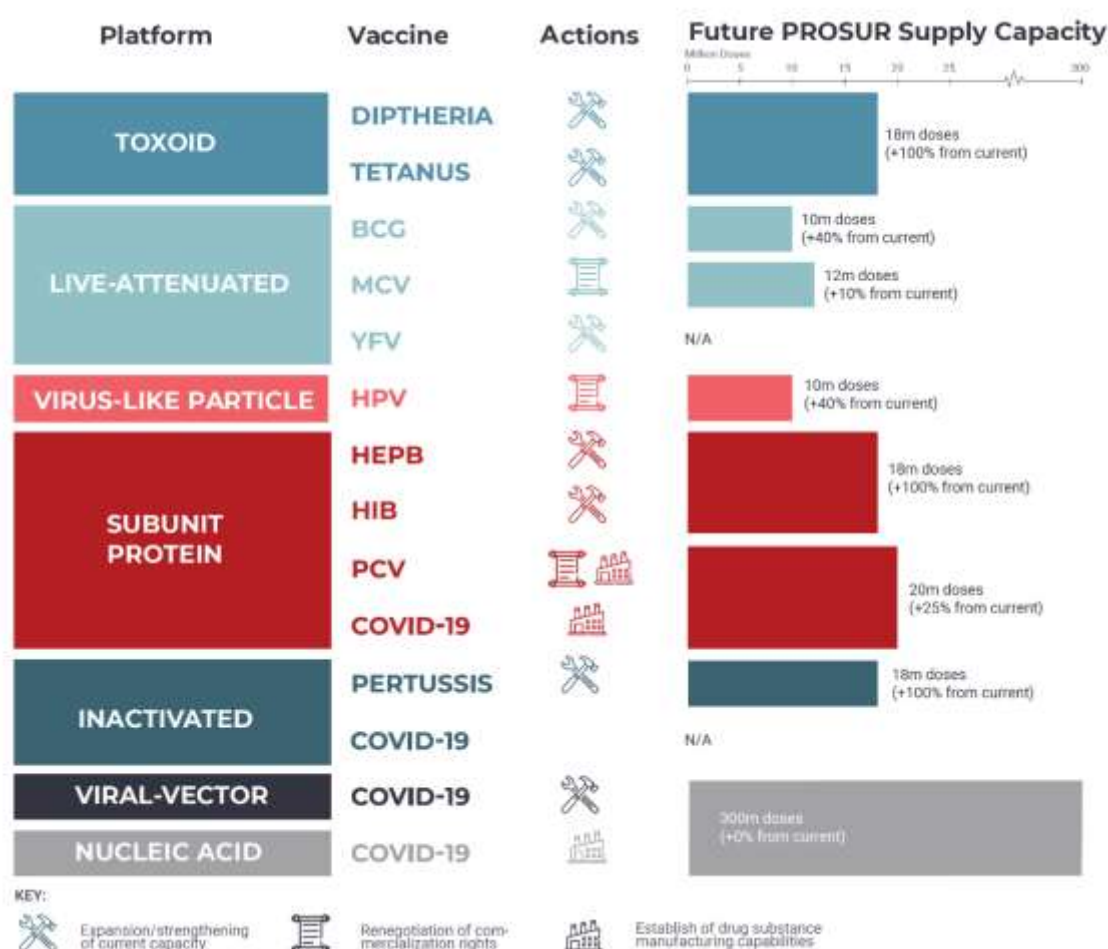
Vaccine manufacturing has been traditionally very concentrated in few large players, mostly located on the North or in India and China. This is the result of the significant economies of scale and know-how barriers to entry in vaccine production. This situation can further worsen the impact of the above factors especially in condition of stress. To overcome those problems, the need for a more distributed vaccine production system is emerging as the appropriate way forward. In this spirit, the PROSUR members states are exploring options to expand vaccine manufacturing in the Latin American region.

Except for HPV, all most important vaccines for routine immunization are well-established in routine immunization programs in the region with high coverage resulting in stable vaccine demand. The situation is structurally different for outbreak-prone diseases such as Measles and Yellow Fever where outbreaks may trigger sudden changes in demand due to vaccination campaigns implemented as part of the response activities. Following roll-out of the primary series, COVID-19 vaccination will be targeting a specific known population, comparable to other routine vaccines and demand dynamics are expected to stabilize. The total demand of Latin American Countries and PROSUR member states for all those vaccines represents a modest share of global vaccine demand. The region therefore has limited leverage to negotiated with suppliers and large variations in demand in other regions can impact access to supply.

From a supply availability standpoint, few COVID-19 vaccines have been developed or are under development in the LAC, compared to other regions, and integrated clinical development and manufacturing of COVID-19 vaccines by manufacturers has been very limited. COVID-19 vaccines production in the region is largely performed by Contract Manufacturing Organizations for vaccine suppliers outside the region and is heavily skewed towards vaccines which employ non-replicated viral vector platform technology. For other key vaccines for the National Immunization Programs, there are few manufacturers in the PROSUR countries capable of developing and producing these vaccines, making the region reliant on technology transfers from manufacturers based outside the region. Those manufacturers are concentrated in Argentina and Brazil. Most of those production activities are the result of technology transfers that have, in most circumstances, constraints in the commercialisation rights, preventing the local producer to serve other countries in the region. As a result, the region is currently not in condition of procuring vaccines from domestic producers and is fully reliant on import of products from outside the region for all key vaccines except for Yellow Fever. Overall, the regional supply-demand balance for vaccines in PROSUR is negative, as available

vaccine produced in the region, are insufficient to meet regional or subregional demand, except for COVID-19 vaccines.

Informed by these findings and based on an assumed goal of achieving regional self-sufficiency with regards to access to supply of selected vaccines, specific recommended actions were developed for each of those vaccines. These recommendations aim at defining the simplest and fastest pathway to enable manufacturers in the PROSUR members to produce sufficiently to fulfil the demand in the subregion for each vaccine.



Collectively, the recommended actions for each vaccine comprise part of a regional strategy to address the fundamental shortcomings in access to vaccines. The strategy considers the technical and market characteristics of each vaccine and the evolving trends in vaccine manufacturing and can be articulated around three areas for action:

1. The **establishment of bulk production manufacturing specific hubs** via the negotiation of technology transfers for the mRNA (already under development with PAHO) and subunit protein platforms. This can serve COVID-19 and PCV vaccine supply needs and lay the foundation for future other vaccines (such as Influenza)
2. The **renegotiation of the commercialization rights** linked to technology transfers for the existing manufacturer in the region to be able to fully address regional demand from the existing local supplier base. This can serve MCV, HPV and PCV supply needs

3. The **expansion/strengthening of the current existing capacity** to secure supply for existing routine and outbreak response vaccines. This pillar can serve BCG, YFV and Pentavalent vaccine

In addition, the establishment of a supportive ecosystem and appropriate coordination mechanisms are required to ensure success to the strategy. A set of five areas will require actions:

- **Licensing:** it is recommended that a 3rd party entity is tasked with supporting the negotiation of licensing agreements with key vaccine innovators (e.g., academia, biotechnology companies) on behalf of PROSUR countries and manufacturers.
- **Regulatory:** investments in regulatory capacity building, will be required to ensure that NRAs in the region can attain the higher maturity levels required to provide stringent oversight on the manufacturing processes for vaccines.
- **Clinical development:** the development of more robust clinical development capabilities, in the form of independent Contract Research Organizations (CROs) and academic institutions will be essential to ensure that effective execution of the required clinical development activities to achieve marketing authorisation.
- **Manufacturing:** the strengthening of the existing regional network of CMOs capable of performing all vaccine manufacturing processes for different types of vaccines will be critical to fast track the implementation of the strategy leveraging existing resources in the region.
- **Manufacturing input:** the success of any vaccine reliance initiative is reliant on access to the key ingredients for the vaccine manufacturing process (e.g., bioreactors, filters, vials, etc.). This capacity is currently missing in the LAC region. It is critical that this gap is addressed. Build-up of regional capacity to produce key vaccine manufacturing inputs can provide other potential economic development opportunities to countries in the region which may not be suitable for investments in vaccine development and manufacturing.

Finally, the availability of a Technical Advisory Committee will be critical to provide independent technical guidance to the many decisions that will need to be taken across multiple domains. PAHO's existing technical advisory bodies can play an important role in this direction.

This set of recommendations provides a general high-level direction and points out to the critical factors that will need to be considered in the subsequent steps aimed at the refinement of a vaccine self-reliance strategy for the PROSUR member states.

Context and introduction

Starting in January 2020 a global pandemic caused by a new viral pathogen, SARS-CoV-2, has caused severe health and economic impact on a fully immunologically naive world population. In absence of preventive or curative measures for COVID-19, mortality, and morbidity rapidly increased. In the last 6 months of 2020, as result of unprecedented research and development efforts and investments across many countries, the first vaccines to prevent COVID-19 were approved by regulators¹ and administered. Since then, more than 30 vaccines have achieved marketing authorization or emergency listing² and more than 9.7 billion doses of COVID-19 vaccines have been distributed globally³. Disappointingly, the distribution of these vaccines has been uneven across the different regions and countries - only 9.6% of people in low-income countries have received at least one dose⁴ - reflecting not only a significant difference in the purchasing power of different countries but also an uneven distribution of the vaccine research, development, and manufacturing capabilities. Most of these capabilities are concentrated in a handful of countries located in Europe, North America, Japan, China, and India, with few other players from the rest of the world. The concentration of these capabilities is even more stark when focusing specifically on the small number of companies that have the in-house development and manufacturing expertise required to take a vaccine from the discovery phase to the commercialization on global scale (i.e., not accounting for all the entities that can perform only a subset of the development or manufacturing processes).

Due to the potential for prolonged constraints in access to COVID-19 vaccines, currently the most important health tool needed to control the pandemic, the need for a swifter access to vaccines has become critical from a political and public health standpoint. As result, many countries have started looking with renewed interest at strategies to establish or strengthen domestic and regional vaccine manufacturing capacity⁵. While such a strategy can be difficult to implement and even more difficult to sustain, the appetite to control the sources of critical health products is growing, particularly for those products required in the event of a pandemic.

In this context, the government of Colombia, in its capacity as Pro Tempore Presidency in 2021 of the Forum for the Progress and Integration of South America (PROSUR) through the Presidential Agency for International Cooperation (APC-Colombia), contributed funding for the implementation of the project “Scaling up of Immunization Capacities in the PROSUR countries”. The project was developed within the Immunization Subgroup⁶ of PROSUR’s Health Group, with the objective of identifying approaches for sustainable production of vaccines in the region in order to generate equitable and timely access for PROSUR countries, both for vaccines used in routine immunization and preparedness for future pandemics. The Inter-American Development Bank (IDB) supported the project by administering and executing the project budgets.

The project consists of two phases. The first phase (July-December 2021) focused on a diagnostic study of existing production capacities and facilities in the region and of the demand for routine and

¹ In August 2020, Sputnik V was the first COVID-19 vaccine to receive authorization from an NRA. In the same month Comirnaty (Pfizer-BioNTech) was the first COVID-19 vaccine to receive authorization from an NRA capable of supporting the UN prequalification.

² https://en.wikipedia.org/wiki/List_of_COVID-19_vaccine_authorizations accessed January 18, 2022

³ Mathieu, E., Ritchie, H., Ortiz-Ospina, E. et al. A global database of COVID-19 vaccinations. Nat Hum Behav (2021) – One World in Data - <https://ourworldindata.org/covid-vaccinations> accessed on January 18, 2022

⁴ Mathieu, E. et al. – cit.

⁵ <https://www.reuters.com/business/healthcare-pharmaceuticals/africa-needs-make-own-vaccines-hurdles-are-high-experts-say-2021-12-07/> accessed on January 16, 2022

⁶ The participating countries of the Immunization Subgroup are Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay and Peru.

pandemic vaccines. This phase also included a study analysing potential regional governance mechanisms to guarantee equitable access to vaccines produced by the PROSUR countries. In the second phase (January-July 2022), a pre-feasibility analysis is expected to be carried out, which will result in a strategic roadmap with the necessary steps to increase vaccine production capacities in the region.

With the objective of providing a body of evidence that can inform PROSUR discussion and preliminary decisions, a situational analysis has been commissioned by MMGH Consulting (MMGH) including:

- An analysis of the regional vaccine demand for COVID-19 vaccine and for the key paediatric vaccines included in the NIP.
- An analysis of the regional sources of supply, including contract manufacturers that perform only a portion of the production process on behalf of third parties, for COVID-19 vaccine and for key paediatric vaccines
- An analysis of the balance between supply and demand
- An analysis of the readiness of countries in the region to receive technology transfers in the vaccine field

The diagnostic work was performed in the final 6 months of 2021 and included 23 countries in South and Latin America, irrespective of their PROSUR membership, to allow developing a comprehensive regional view of vaccine supply and demand⁷.

In addition to COVID-19 vaccines, additional vaccines have been included in the diagnostic work covering all the key time points in which the NIP delivers vaccines on a regular basis to a defined population:

- Birth dose: BCG vaccine (Bacillus Calmette-Guerin vaccine against tuberculosis)
- Doses delivered in the first 9 months of life: Pentavalent vaccine (DTP-HepB-Hib combination vaccine against Diphtheria, Tetanus, Pertussis, Hepatitis B, Hemophilus Influenza Type B) and PCV Vaccine (Pneumococcal Conjugate Vaccine)
- Doses delivered from 9 to 24 months: MMR/MMR-V (Measles-Mumps-Rubella and Measles-Mumps-Rubella-Varicella vaccine) and Yellow Fever vaccine
- Doses delivered from 9 to 14 years: HPV vaccine (Human Papilloma Virus vaccine)

Measles and Yellow Fever vaccines also provided a view on the demand for vaccines aimed at the prevention of and response to diseases with outbreak potential.

Based on the outcome of the analyses and of the discussions with the PROSUR countries, a set of preliminary expert recommendations detailing a potential way forward has been formulated by the MMGH team. This report provides a detailed overview of the analyses, of the methodologies employed and of the emerging recommendations. Read in combination with the governance assessment, it provides the foundation for the subsequent pre-feasibility analysis scheduled for 2022.

⁷ Small Caribbean islands have been excluded considering their very limited impact on the total regional demand and their limited impact on vaccine manufacturing capacity sizing decisions.

Vaccine demand

Different estimates of vaccine demand exist depending on the specific questions the forecasting work needs to answer. Procurement decisions are generally informed by short term operational forecasts that captures detailed short-term view of each country needs (e.g., stock keeping units between 12-36 months). Operational forecasts consider the consumption and ordering patterns, the existing level of product stocks, and any other operational factor that can influence consumption by the immunization program. Vaccine developer and manufacturer decisions informing clinical development and manufacturing capacity investments as well as public sector decision on budget and long-term immunization program capacity rely instead on high-level (vaccine level) longer term strategic demand forecasts (e.g., 10-year or 20-year time horizon). This second type of forecasts are based on high-level population and vaccination coverage estimates as well as on standardized parameters (i.e., wastage rates, buffer stock levels, etc.) to forecast the dynamics of program demand.

This diagnostic analysis focuses on identifying the high-level vaccine manufacturing needs for the Latin American and Caribbean (LAC) region; for this reason, it adopts a strategic demand forecast approach. As result, the country demand for each vaccine is estimated by defining a set of assumptions on a few key programmatic aspects:

- a) The **size of the population targeted** – consequence of the epidemiology of the disease and of the adoption decision of the country which determines the population vaccinated and the timing for the vaccination program start.
- b) The **characteristics of the specific vaccine** – its administration schedule, its indication and its presentation which determines the number of doses required and its average open vial-wastage, thereby influencing the target population that can be served.
- c) The **performance of the immunization program** – that determines the coverage and the closed-vial wastage as well as the required level of buffer stock that needs to be maintained in the system.

At the time of introduction of a new vaccine into the NIP, vaccine demand can vary substantially depending on its ramp-up and the timing of the roll-out. Once the introduction phase has been completed, if the health systems are sufficiently strong to reach a high coverage, the demand stabilizes unless supply constraints occur limiting the capacity of the program to reach the target population. An exception is represented by vaccines for diseases with outbreak potential where supplementary immunization activities (SIAs) aimed at reducing the number of susceptible individuals and/or for immediate outbreak response can cause significant variability in the overall demand.

The countries which are a member of the Pan American Health Organization (PAHO), among which the PROSUR countries are included, have historically been successful in the introduction of new vaccines, in particular the vaccines which are cornerstones of the Expanded Program on Immunization (EPI). Currently, all key vaccines in the infant immunization schedule relevant for the LAC region are introduced and have achieved a high coverage level; therefore, demand for these vaccines is stable. For the reasons mentioned in the introduction, the COVID-19 vaccine roll-out is still unfolding and only in 2023 is the annual demand expected to stabilize.

Methodology

Vaccine demand estimates have been developed at individual level for the 23 countries in Central America, South America, and the Caribbean for 6 of the 7 vaccines in scope (the HPV vaccine

forecast was developed differently as described below). For each vaccine, the forecast is aimed at defining the steady state demand (i.e., the normal demand that needs to be fulfilled once a vaccine program is scaled and has achieved desired coverage) and did not include any specific event or dynamic that could be a one-time occurrence. The following basic formula was used to estimate the steady state vaccine dose requirements:

$$(Target\ population \times 2019\ coverage\ (per\ dose)) \times (1 + wastage\ rate)$$

Where:

- Target population was sourced from the Population Division of the Department of Economic and Social Affairs of the United Nations⁸ for new-borns (BCG, DTP-containing and PCV vaccines), 1st year of life (Measles-containing and Yellow Fever vaccines), over 65 (PCV vaccine's elderly dose) and for the entire population (COVID-19 vaccine). In view of the moderate growth rate in the region the 2020 values have been taken as reference for this rapid diagnostic and no growth rate applied.
- Coverage estimates were sourced from WHO-UNICEF estimates (WUENIC)⁹; 2019 coverage estimates were used instead of the most recent 2020 to avoid potential bias caused by the impact of the SARS-CoV-2 pandemic.
- Coverage for the second dose was interpolated linearly from the coverage for the available estimates of the first and the third dose (for Pentavalent and PCV)
- The coverage of the first dose of DTP-containing vaccines was used as proxy for the coverage of the first dose of PCV (for which only the coverage of the third dose is available in WUENIC)
- No growth rate was assumed for the coverage for the future years, the LAC region having already achieved high coverage levels across all vaccines
- Standard wastage rates as per WHO guidance¹⁰ were used
- No buffer stock calculation was included for all programs being in a steady state.

For HPV vaccine, the WHO's latest MI4A demand estimates for the year 2030 were used¹¹. Those estimates were used instead of the approach used for the other vaccines because the HPV program has yet to reach its steady state. As of December 2021, only 112 countries have introduced HPV vaccine into their NIP. Supply constraints have delayed introduction and impaired coverage uptake, and the current dose consumption is on average lower than the future steady state. By projecting demand until 2030 based on a set of assumptions for country introduction dates and coverage ramp up, the MI4A forecast provides a reasonable estimate of the steady state dose requirements once the program will have reached its steady state in LAC countries.

Five of the 8 PROSUR countries (Brazil, Colombia, Chile, Peru, Paraguay) provided the historical dose requirements for each vaccine in their NIP for 2020-2021 and estimates for the following 2 years.

⁸ <https://population.un.org/wpp/> accessed on December 10, 2021

⁹ <https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/global-monitoring/immunization-coverage/who-unicef-estimates-of-national-immunization-coverage> accessed on December 10, 2021

¹⁰

https://www.who.int/immunization/programmes_systems/supply_chain/resources/Guide_Global_WHO_Vaccine_Wastage_tool.pdf accessed on December 10, 2021

¹¹ <https://www.who.int/publications/m/item/who-hpv-vaccine-global-market-study-november-2020> accessed on December 10, 2021

Brazil provided also demand estimates for the COVID-19 vaccine. After discussion with the countries and clarification of the underlying assumptions, those estimates were incorporated (the last projected year or the average of last 3 if demand was not stable) replacing the generic estimates. No major discrepancies were recorded.

Total estimates for PROSUR and for the entire LAC region were defined by consolidating the country provided data with the forecasts for the remaining countries. The outcome of the analysis is described below.

Regional demand for COVID-19 vaccines

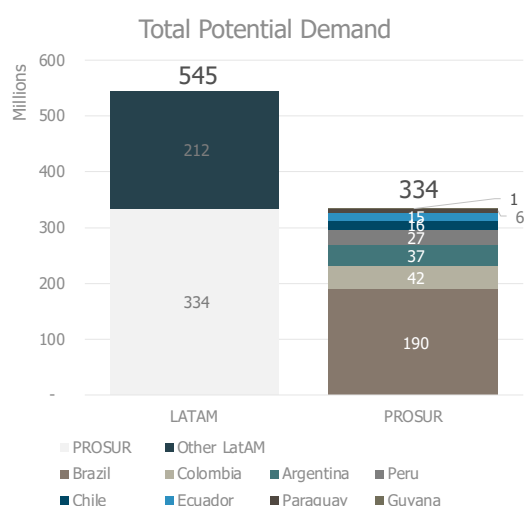
COVID-19 vaccine demand estimates were based on the key assumption that the primary series roll-out will be completed, overcoming the existing supply constraints in all countries in the region by the end of 2022, allowing for vaccination of the entire population older than 1 year of age. Future demand for COVID-19 vaccine will be limited to booster doses.

The assumption of a yearly booster was taken to develop the demand estimates. An average coverage of 80% was assumed for all countries. A single dose presentation was assumed for the future and a 5% wastage assumption was employed. Since the vaccine roll-out is already assumed (i.e., primary series) and a steady state achieved, no buffer stocks were assumed. Such an assumption will also hold in the event of updated versions of COVID-19 vaccines being rolled out to provide better protection against emerging variants. Since the ramp-up of the new versions will never be instantaneous, leading to the immediate discard of the older doses, it can be assumed that a progressive substitution of the doses of older versions of the vaccine will take place in parallel, leading to use of different types of vaccines for a certain period.

A total **LAC regional demand of 545 million doses of COVID-19 vaccine** was estimated (Figure 1); this represents approximately 8% of the future global booster demand of approximately 6.5 billion doses. It is worth highlighting that as per end of January 2022, PROSUR countries have been accessing COVID-19 doses largely via bilateral deals or from domestic supply with only marginal contributions from COVAX¹². Of the total LAC demand, **334 million doses originated from the 8 PROSUR countries**. Fully driven by population size, with coverage being considered equal across countries, Brazil represents the largest share of demand, comprising more than 50% of PROSUR demand. Demand from Colombia, Argentina and Peru are subsequently the most sizeable among PROSUR countries.

Figure 1: COVID-19 vaccine demand in PROSUR and LAC countries

¹² IMF-WHO COVID-19 Vaccine Tracker – <https://www.imf.org/en/Topics/imf-and-covid19/IMF-WHO-COVID-19-Vaccine-Tracker> - accessed on January 2022



Regional demand for routine vaccines

Applying the above-described methodology, demand estimates were also generated for the key routine vaccines included in NIPs.

BCG Vaccine

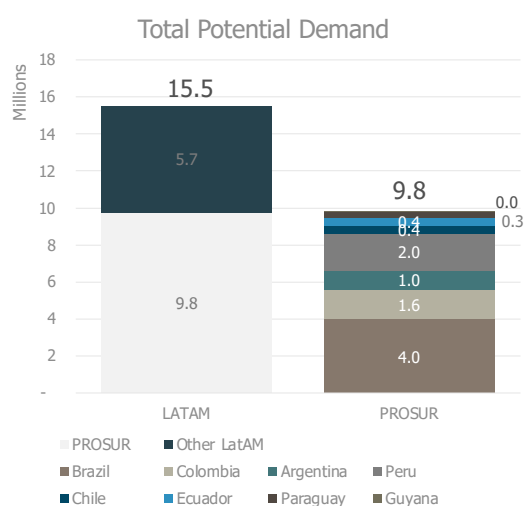
The BCG vaccine against tuberculosis is an old vaccine that has been in use for almost 100 years; it is fully rolled-out in the LAC region and has achieved a steady state of implementation. The vaccine is administered at birth¹³ with a single dose and has high coverage with 2019 data showing a range of 79-99% coverage range in the PROSUR countries and a 73-99% range in the rest of the LAC region. All presentations in use are high multi-dose (10 or 20 dose) with a corresponding high wastage rate of 50%.

The total **LAC regional demand was estimated at 15.5 million doses** (Figure 2); this represents approximately 5% of the global demand of 325 million doses¹⁴. Of those, 9.8 million doses are consumed by PROSUR countries. Among the PROSUR countries, Brazil represents approximately 40%, followed by Peru and Colombia. It is important to observe that share of demand of the same country is not only driven by population numbers but may vary depending on the epidemiology / endemicity of the disease, differences in policies and procurement practices.

Figure 2: BCG vaccine demand in PROSUR and LAC countries

¹³ Tuberculosis (BCG) vaccines: WHO position paper – February 2018 - Weekly epidemiological record; No 8, 2018, 93, 73–96

¹⁴ 2018 global demand estimates from WHO's BCG vaccine Market Study - <https://www.who.int/publications/m/item/who-bcg-vaccine-global-market-study-may-2019> accessed on December 2021



Pentavalent vaccine (DTP-containing)

The pentavalent vaccine is a combination of five vaccines for the prevention the following diseases: Diphtheria, Pertussis, Tetanus, Hepatitis B and Hemophilus influenza type B. Different versions of the vaccine exist depending on the type of pertussis vaccine used (i.e., acellular, or whole cell).

Furthermore, some countries¹⁵ may also use an extended combination including also inactivated polio vaccine (IPV). The vaccine has been in use in different combination forms for several decades and is fully rolled-out across the LAC region and has achieved a steady state of implementation. Future changes in presentation or formulation (e.g., switching from Pentavalent to Hexavalent) are not expected to cause significant changes in demand. The vaccine is administered with a 3-dose schedule during the first year of life at 6, 10 and 14 weeks¹⁶. Very high vaccination coverage has been achieved across the PROSUR countries (e.g., DTP1 coverage ranged between 81-99% in 2019, with an average drop-out rate of 3.4%) and in the other Latin American countries (e.g., DTP1 coverage ranged between 75-99% in 2019, with an average drop-out rate - the coverage difference between the first and last dose of vaccine - of 6.3%). Vaccines with low multi-dose presentations (1 to 5 doses) are used with and an average wastage rate is estimated at 10%.

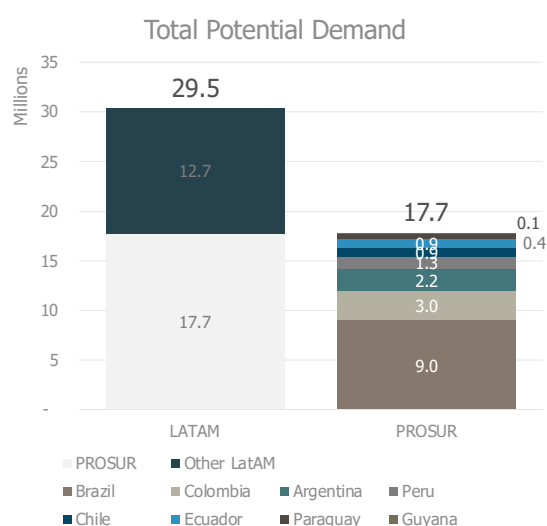
The total **LAC regional demand was estimated at 29.5 million doses** (Figure 3); this represents approximately 8% of the global demand of 390 million doses¹⁷. Of those, 17.7 million doses are consumed by PROSUR countries. Among the PROSUR countries, Brazil represents approximately 50% of the subregional demand, followed by Colombia and Argentina.

Figure 3: Pentavalent vaccine demand in PROSUR and LAC countries

¹⁵ Chile uses Hexavalent vaccine; Brazil is procuring some doses of Hexavalent

¹⁶ Information on Pentavalent can be retrieved in each of the 5 individual vaccines composing the combination. Information used on this report are source from the Diphtheria position paper. Diphtheria vaccines: WHO position paper – August 2017, Weekly epidemiological record; No 31, 2017, 92, 417–436

¹⁷ 2018 global demand estimates from WHO's DTP-containing vaccines Market Study - <https://www.who.int/publications/m/item/who-d-t-containing-vaccines-global-market-study-may-2019> accessed on December 2021



Pneumococcal Vaccine

The Pneumococcal Vaccine for the prevention of Pneumococcal Pneumonia has two different versions: the older polysaccharide (PPS) vaccine not suitable for infants with short duration of protection and the conjugate vaccine (PCV) providing prolonged protection and suitable for the EPI program. Different versions of the PCV vaccine are available with different levels of serotype coverage or valency (10 to 20 different serotypes can be covered by different licensed vaccines). With the extension of the indication of PCV to the elderly, the polysaccharide vaccine is progressively being replaced also in the older age group. PCV has been almost fully rolled out in the EPI programs across the entire LAC region in the past 15 years. All PROSUR countries have rolled out PCV while a handful of countries in the rest of the LAC still must introduce and scale the vaccine in their EPI programs (Cuba, Belize, Venezuela, and Suriname). The estimates of steady state demand include the completion of the roll-out in the above-mentioned countries and demand generated for the elderly population (i.e., above 65 years).

PCV is administered with a 3-dose schedule during the first year of life at 6, 10 and 14 weeks¹⁸. Similarly, to DTP-containing vaccines, with whom PCV is co-administered, a very high coverage level has been achieved across the PROSUR countries (in 2019, PCV1 coverage ranged between 84-99% and PCV3 coverage ranged between 84-98%) and in the other Latin American countries (PCV1 coverage ranged between 75-99% in 2019, while PCV3 coverage ranged between 42-99%). A nominal demand corresponding to 5% of the over 65-year-old population has been assumed with one single dose being administered to capture demand from the elderly population irrespective of the existence of a national recommendation (no country in the region has a formal recommendation for elderly). Vaccines with low multi-dose presentations (1 to 4 doses) are used with an average wastage rate estimated at 10%.

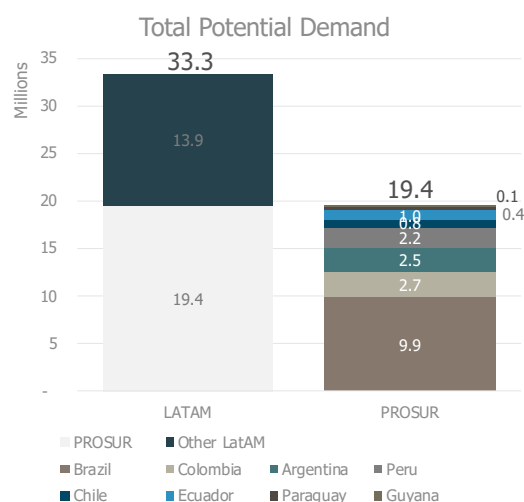
The total **LAC regional demand was estimated at 33.3 million doses** (Figure 4); this represents approximately 14% of the global demand of 245 million doses¹⁹, a higher number compared to DTP since the global PCV roll-out is still in-progress. Of those, 19.4 million doses are consumed by

¹⁸ Pneumococcal conjugate vaccines: WHO position paper 2019 - Weekly epidemiological record, No 8, 2019, 94, 85-104; Considerations for pneumococcal vaccination in older adults - Weekly epidemiological record, No 23, 11 June 2021

¹⁹ 2019 global demand estimates from WHO's Pneumococcal Vaccines Market Study - <https://www.who.int/publications/m/item/who-pneumococcal-vaccines-global-market-study-june-2020> accessed on December 2021

PROSUR countries. Among PROSUR countries, Brazil represents approximately 50% of the subregional demand, followed by Colombia and Argentina. No demand is assumed for polysaccharide in the long-term.

Figure 4: PCV vaccine demand in PROSUR and LAC countries



Measles Mumps Rubella (MMR) and Measles Mumps Rubella Varicella (MMR-V) vaccines

Multiple different measles-containing combination vaccines are available on the market; four are the most commonly used: measles monovalent, measles-rubella combination (MR), measles-mumps-rubella (MMR) and measles mumps rubella varicella combination (MMR-V). The latter two are the vaccines primarily used in PROSUR countries and in the LAC region. The simpler combinations have been in use for several decades while more complex MCVs have been introduced more recently into routine immunization schedules. All countries in the LAC region have completed the roll-out of MCVs in the NIP and have achieved a steady state of implementation.

The vaccine is administered with a 2-dose schedule at 9 and 18 months²⁰. A very high coverage level has been achieved across the PROSUR countries (MCV1 coverage was between 83-98% and MCV2 coverage was between 66-92% in 2019) and in the other Latin American countries (MCV1 coverage was between 65-99% and MCV2 coverage was between 41-99% in 2019^[20]). Vaccines with either a 5 or 10-dose presentation are used with an average wastage estimated at 25%. Some coverage gains may still be achieved in the future which could result in increases in the overall demand for MCV in the region.

The total **LAC regional demand was estimated at 19 million doses** (Figure 5); this represents approximately 16% of the global MMR-MMRV demand of 115 million doses²¹; the higher proportion of the regional demand on the global one is the result of the still predominant global use of MR combination. PROSUR countries were estimated to consume 10.5 million doses. Among the PROSUR countries, Brazil represents approximately 50% of the subregional demand, followed by Argentina and Colombia. Outbreak demand is not forecasted in view of its limited size and difficulty to accurately forecast.

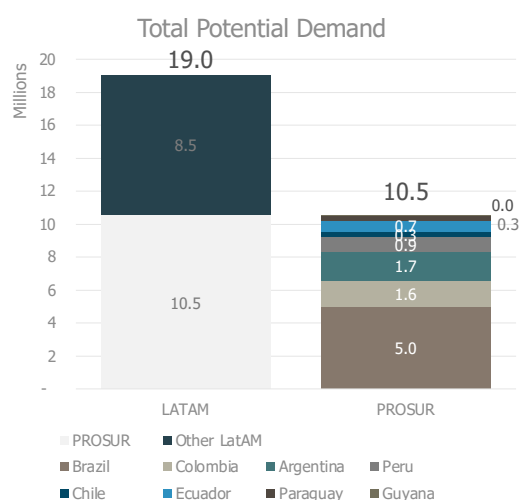
²⁰ WHO position papers on Measles, Weekly Epidemiological Record, 2017, vol. 92, 17

²¹ 2020 global demand estimates from WHO's Measles-containing vaccines market study -

<https://www.who.int/publications/m/item/who-measles-containing-vaccine-global-market-study---july-2020>

- accessed on December 2021

Figure 5: MCV vaccine demand in PROSUR and LAC countries



Human Papilloma Virus (HPV) vaccine

The human papilloma virus (HPV) vaccine against cervical cancer is currently being rolled out globally²². The roll-out of HPV has been delayed by significant supply constraints that caused many countries to postpone planned introductions. All countries in PROSUR have now introduced HPV for eligible female populations, while only Argentina, Brazil and Guyana have also introduced in males. In the broader LAC region, Venezuela has not yet introduced the HPV and most other countries are only administering HPV vaccines to eligible females and have not yet begun to vaccinate males in the same age group.

HPV is administered with a 2-dose schedule to girls and boys, primarily in HICs and UMICs, between 9 and 14 years of age²³ through school programs or health-facility based immunization sites. Vaccination coverage for HPV is lower than coverage for routine vaccines targeting infants because of the more challenging delivery strategy, reduced level of community awareness, and increased vaccine hesitancy. HPV is available in low, multi-dose presentation (1-2 doses) and an average wastage rate of 10% has been assumed.

In relation to the HPV vaccination schedule, it is important to note that clinical studies are ongoing using some of the currently licensed HPV vaccines to assess the protection conferred by a single dose schedule²⁴. Should the protection offered by a single dose of HPV be found to be non-inferior to a 2-doses schedule, it is anticipated that the total demand for HPV vaccine will be reduced by 50% once countries adopt the revised HPV vaccination schedule.

As HPV vaccine rollout and implementation is at an earlier stage compared to the other infant vaccines, HPV demand in 2030 has been estimated to better represent the future steady state of the HPV program. It is assumed that supply and other constraints will be fully overcome by then and the vaccine will be fully rolled out in all countries in the region. The 2030 demand forecast has been obtained from the most recent market analysis performed by the WHO's MI4A initiative²⁵ which

²² As of December 2021, 112 countries have introduced HPV into their NIP.

²³ WHO position papers on Human papillomavirus (HPV), Weekly Epidemiological Record, 2017, vol. 92, 19

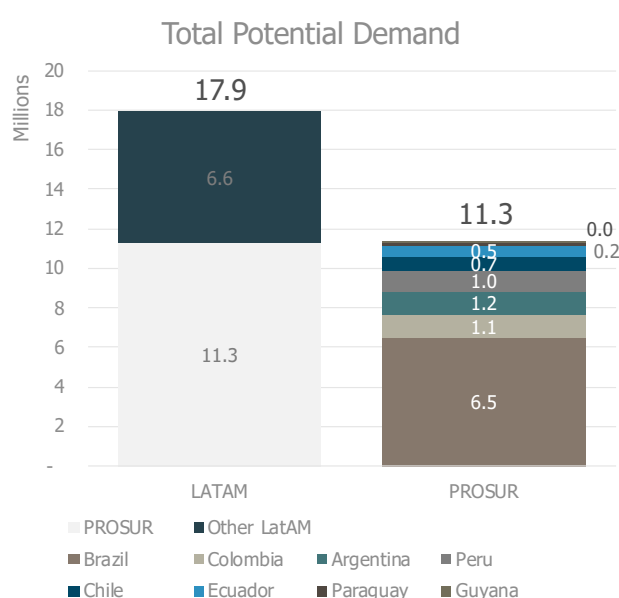
²⁴ A Single-Dose HPV Vaccine Evaluation Consortium including 8 independent research institutions has been formed in 2018 to collate and synthesize existing evidence and evaluate new data on the potential for single-dose HPV vaccination - <https://www.path.org/resources/working-together-evaluate-evidence-single-dose-hpv-vaccination/> accessed on January 2022

²⁵ Data not published

incorporates the up-to-date information on HPV supply and provides projections for the year 2030 for both boys' and girls' demand using a 2-doses schedule.

The total **LAC regional demand was estimated at 17.9 million doses** (Figure 6); this represents approximately 12% of the global demand of 150 million doses²⁶. Of the total demand, 11.3 million doses are estimated to be consumed by PROSUR countries. Among the PROSUR countries, Brazil represents approximately 55% of the subregional demand, followed by Argentina and Colombia. Demand from countries which are vaccinating both girls and boys represents 76% of total demand in the LAC region and an additional 4.3 million doses of HPV are forecasted to be added to the regional total once additional countries begin to administer HPV to boys as part of the routine schedule.

Figure 6: HPV vaccine demand in PROSUR and LAC countries



Yellow Fever vaccine

The vaccine for the prevention of yellow fever has been in use for ~100 years and it has been rolled out in all countries where the yellow fever remains an endemic disease. The yellow fever vaccine is administered to infants at 9 months of age with a single dose which does not require further boosting²⁷. The available vaccine presentations are high, multi-dose (10-20 doses) and a 50% wastage rate is assumed.

High vaccination coverage with yellow fever vaccines has been achieved in areas targeted with the vaccine, either nationally or sub-nationally, based on local yellow fever epidemiology. Countries using the vaccine sub-nationally report lower national vaccination coverage because the vaccine is being used in a subset of the national population. Within PROSUR countries, yellow fever vaccination coverage²⁸ ranges between 8-94% while in the other few endemic LAC countries vaccination coverage ranges between 7-80%.

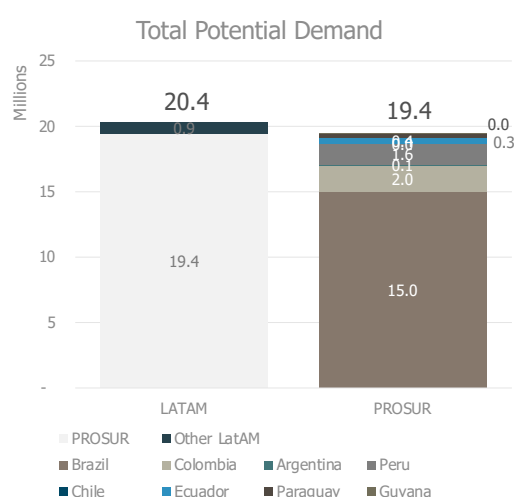
²⁶ 2030 global demand estimates from WHO's HPV vaccine market study - <https://www.who.int/publications/m/item/who-hpv-vaccine-global-market-study-november-2020> - accessed on December 2021

²⁷ Vaccines and vaccination against yellow fever: WHO Position Paper – June 2013 - Weekly Epidemiological Record, 88 (27): 269 - 283

²⁸ 2019 data

The total LAC demand was estimated at 20.4 million doses (Figure 7); with 19.5 million doses consumed by PROSUR countries. Among PROSUR countries, Brazil represents approximately 75% of the subregional demand, followed by Colombia and Peru. Some uncertainty exists on the long-term size of the demand for Yellow Fever vaccines in view of (a) the stagnation of the PAHO program for fighting yellow fever; (b) the impact of global warming that can alter the breeding area for the vector (the *Aedes aegypti* mosquito) potentially expanding it currently non-endemic areas. A specific demand estimate for outbreak response is not included due to the high unpredictability of outbreaks and the high coverage achieved in the endemic areas which reduces the likelihood of outbreaks. A global stockpile exists which provides emergency doses in the event of large outbreaks.

Figure 7: Yellow Fever vaccine demand in PROSUR and LAC countries



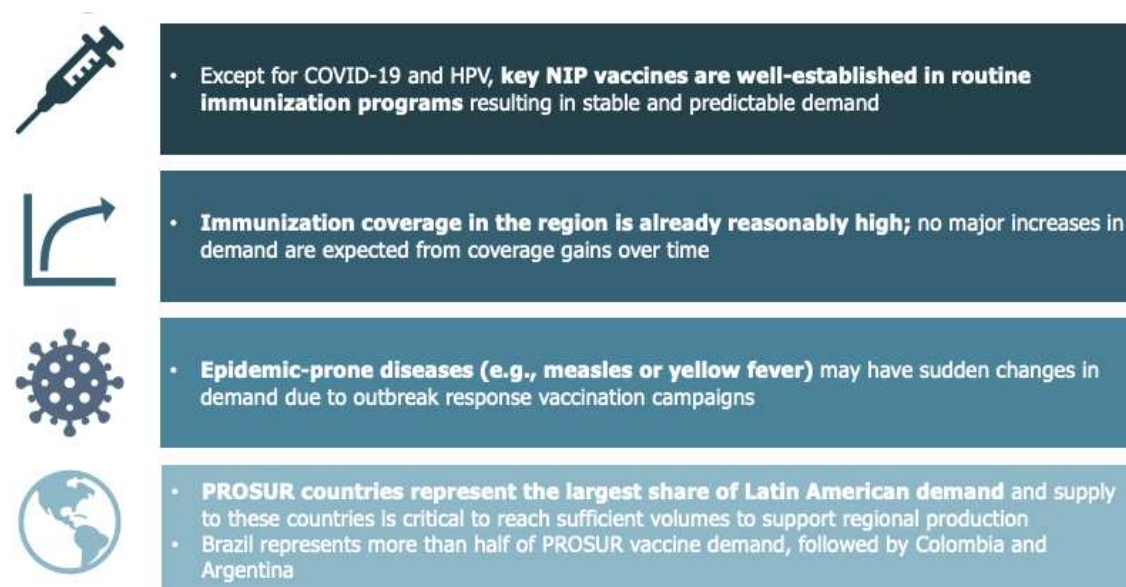
Conclusions

Based on the demand of each of the vaccines assessed in both PROSUR countries and in the broader LAC region some general conclusions can be made which are summarized below and in Figure 8:

- **Except for COVID-19 and HPV, key NIP vaccines are well-established in routine immunization programs, resulting in stable vaccine demand.** Uncertainty around COVID-19 demand is primarily related to the type of vaccine required due to the potential emergence of variants, and particularly for the need of different versions of the currently available vaccines. Uncertainty around HPV demand is related primarily to: (a) the extent in which gender-neutral policies will be rolled out beyond the countries that currently have those policies in place; (b) the outcome of the single-dose studies that, in case of successful outcomes, may lead to reduced demand.
- **Immunization coverage in the region is already reasonably high and no major increases in demand are expected from coverage gains over time.**
- **Outbreak-prone diseases may trigger sudden changes in demand due to vaccination campaigns implemented as part of outbreak response activities.** Measles and Yellow Fever can contribute to sudden fluctuations in demand that are difficult to forecast. For this reason, shortages of those vaccines have been experienced periodically. Global or regional stockpiles can support NIP needs and help to meet programmatic needs in times of demand volatility. Following roll-out of the primary series, COVID-19 vaccination is targeting a specific known population, comparable to other routine vaccines and demand dynamics are expected to stabilize.

- **The total LAC demand represents a modest share of global vaccine demand.** The region therefore has limited leverage to negotiated with suppliers and large variations in demand (especially for outbreak prone diseases) in other regions can impact access to supply.
- **PROSUR countries represent the largest share of LAC demand.** The consolidated demand of these countries is critical to reach sufficient volumes to support any regional plan for production of vaccines with the required economies of scale.
- **Brazil represents more than half of PROSUR vaccine demand, followed by Colombia and Argentina.** Similarly, to the position of PROSUR in relation to the LAC region, Brazil is critical to the viability of any demand-driven vaccine manufacturing strategies.

Figure 8: Summary of conclusions regarding vaccine demand in PROSUR and LAC



Analysis of regional vaccine supply

The development and manufacturing of vaccines is a challenging, high-risk, and capital-intensive endeavour that requires specialized expertise in clinical development, vaccinology, regulatory, and large-scale biological product manufacturing. As result of those factors, there are a limited number of public and private entities globally with the capacity to develop a vaccine from the discovery phase to global commercialization. COVID-19 vaccines represent an exception to the general concentration of the vaccines markets. As per January 2022, there are at least 30 vaccines that have received at least emergency use authorization. One other difference related to COVID-19 vaccines is the large use of contract manufacturing organizations (CMO) to allow the unprecedented ramp up of vaccine manufacturing capacity required to respond to the SARS-CoV-2 pandemic. Finally, the speed at which development of COVID-19 vaccines represents a paradigm shift in how the global immunization community can approach future vaccine development and approval. Future supply of vaccines will be impacted by those changes.

To understand the regional vaccine supply situation, both with regards to COVID-19 and pre-existing vaccines used in routine immunization programs, an assessment of the current vaccine development and manufacturing ecosystem in the LAC region was performed, including mapping of existing local vaccine manufacturers, their associated product portfolios and vaccine platform technologies, and quantification of production capacities.

Based on the findings of the landscape analysis, strengths and weaknesses were determined based on the current regional vaccine manufacturing capabilities to highlight areas of potential focus for a PROSUR vaccine manufacturing initiative. To identify synergies, areas of collaboration and emerging consensus regarding best practices for vaccine manufacturing for future pandemic preparedness, a review of other regional vaccine manufacturing initiatives was also performed. Collectively, these data sources and analyses enabled both quantitative and qualitative assessment of the vaccine manufacturing ecosystem in the LAC region and the potential gaps for a PROSUR initiative to address to improve regional vaccine supply sustainability.

Regional development and manufacturing for COVID-19 vaccines

Methodology

A review of public information sources was first performed to identify COVID-19 vaccine developers and manufacturers based in the LAC region. Information sources included but were not limited to WHO's COVID-19 vaccine tracker and landscape²⁹, publications from COVAX³⁰, CEPI³¹ and the Duke Global Health Innovation Center³² as well as press releases from relevant pharmaceutical companies. Information was consolidated regarding each vaccine manufacturer, their role in COVID-19 vaccine development (i.e., development, manufacturing, or contract manufacturing), status of pipeline COVID-19 vaccines under development, contracts, or licensing agreements with other pharmaceutical companies with COVID-19 vaccine intellectual property, manufacturing capabilities and product-specific production capacities. PROSUR member states were also surveyed and provided inputs regarding domestic vaccine ecosystem, identifying local vaccine developers and manufacturing entities.

The analysis has mostly collected information on the potential capacity that manufacturer can make available or have contracted based on their current knowledge of the new processes and of their resources' requirements. A unique perspective from the one adopted for the routine vaccines where the focus has been, in view of the established and well-known processes and market dynamics, on the effective available supply.

This information was subsequently used to develop a regional situation analysis of vaccine developers and manufacturers in the LAC region. It also served as base to generate high-level estimates of COVID-19 vaccine production capacity for each manufacturer in the region, which were aggregated to estimate the total vaccine manufacturing capacity for COVID-19 vaccines in the LAC region, as well as by vaccine platform technology (e.g., messenger RNA, non-replicating viral vector, protein subunit, inactivated).

Results

As per January 2022, an unprecedented number of COVID-19 vaccine clinical development programs is in place, with over 120 pipeline candidates³³ being developed and evaluated globally. The vast majority of active COVID-19 vaccine clinical development programs can be found in the United States, China, the European Union, the United Kingdom, India, South Korea, and Japan. The clinical development of COVID-19 vaccines outside of these areas is far more limited as illustrated in Figure 9. This uneven distribution has played a role in the COVID-19 vaccine access issues experienced in

²⁹ WHO COVID-19 vaccine tracker and landscape (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>)

³⁰ <https://www.gavi.org/covax-facility>

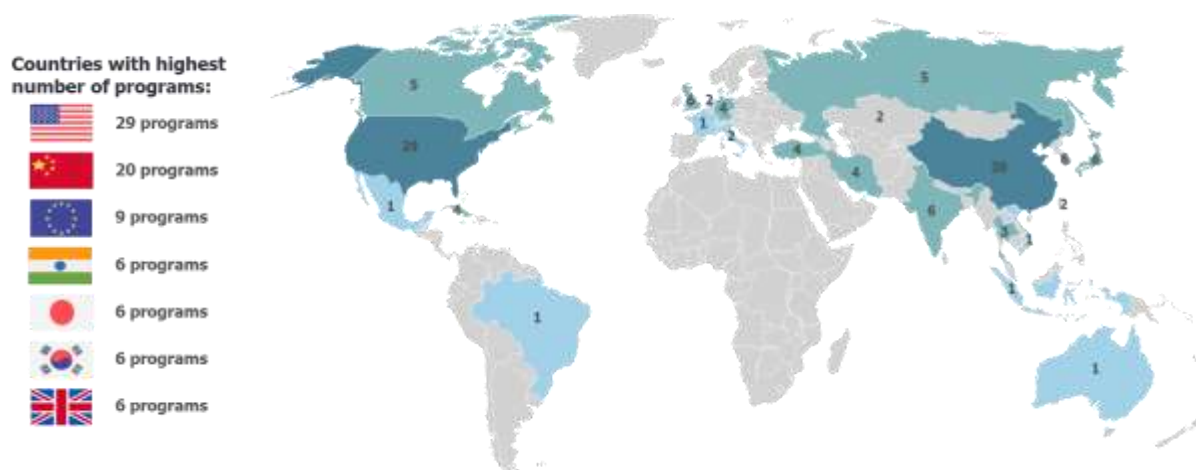
³¹ <https://cepi.net/covax/>

³² <https://launchandscalefaster.org/covid-19/vaccinemanufacturing>

³³ WHO COVID-19 vaccine tracker and landscape accessed on September 24, 2021

many regions of the world. COVID-19 vaccines that have received regulatory approval, differentiated by the platform technology they employ are detailed in Annex 1.

Figure 9: Active clinical development programs for COVID-19 vaccines



In the LAC region, there are currently 6 COVID-19 vaccine clinical development programs in operation. Those are being led by 5 different vaccine developers and manufacturers, representing 5% of active clinical development programs globally. These clinical development programs are being led by manufacturers based in Brazil, Cuba, and Mexico, using RNA, protein subunit and inactivated vaccine platform technologies. Of the 5 COVID-19 vaccine developers in the LAC region, 3 have prior experience developing and manufacturing vaccines, each possessing existing licensed vaccine within their respective product portfolios. Among the vaccines developed in the LAC region, only 2 vaccines, the ones developed by Center for Genetic Engineering and Biotechnology and Instituto Finlay, both based in Cuba, have attained regulatory authorization³⁴. Biomanguinhos Fiocruz, based in Brazil, also recently received regulatory approval for all manufacturing processes of AstraZeneca/Oxford COVID-19 vaccine, based on a technology transfer initiated in 2021³⁵.

To-date, the COVID-19 vaccines being developed by developers based in PROSUR member states have not been approved by national regulators for use. Figure 10 provides a detailed view of the COVID-19 vaccine development landscape in the LAC region.

Figure 10: COVID-19 vaccine development in the LAC region

³⁴ The COVID-19 vaccine manufactured by the Center for Genetic Engineering and Biotechnology is currently licensed in 4 different countries, while the vaccine produced by Instituto Finlay is licensed for use in 3 countries.

³⁵ <https://portal.fiocruz.br/en/news/fiocruz-receives-register-100-brazilian-covid-19-vaccine> accessed on January 2022



While the development and commercialization of COVID-19 vaccines by developers in the LAC region has been limited, other vaccine manufacturers and pharmaceutical companies based in the region have played a significant role as CMOs, producing vaccines developed outside the region, to help enable LAC access to COVID-19 vaccines. These CMOs are executing various parts of the vaccine manufacturing process based on 1) their existing capabilities and 2) the contractual agreements negotiated with the pharmaceutical companies which possess the intellectual property for COVID-19 vaccines developed outside the LAC region. Specifically, manufacturers are performing drug substance or bulk production processes, whereby the vaccine antigen is produced, or formulation, fill, and finish processes, where the vaccine antigen is combined with stabilizers and preservatives to create drug product and filled into vials for packaging and distribution.

Within the LAC region, there are 3 different CMOs producing vaccine drug substance, mAbxience and Biomanguinhos Fiocruz both performing this function for the AstraZeneca/Oxford vaccine, and Uniao Quimica producing the Sputnik V vaccine developed by the Gamaleya Institute. Based on publicly available information, it is estimated that the combined production capacity of these CMOs is ~306 million vaccine doses per year. These contract manufacturers therefore provide the LAC region and PROSUR member states with a strong manufacturing base for non-replicating viral vector vaccines. Additionally, there are 7 different CMOs performing the fill and finish processes for 3 non-replicating viral vector COVID-19 vaccines, 2 inactivated vaccines and 1 mRNA vaccine. Together, these companies have an estimated fill and finish capacity of ~333 million vaccine doses per year. Figure 11 provides a detailed summary of the entities performing contract manufacturing functions in the LAC region.

Figure 11: COVID-19 contract manufacturing organizations in LAC region, by vaccine originator³⁶

³⁶ Manufacturers in bold text are those based in LAC region.

Originator	 Fill & Finish	 Bulk	 Bulk + Fill & Finish
Astra Zeneca	Amri – Catalent – CP Pharma – Daiichi-Sankyo – Insud Pharma – KMB – Meji – Wockhardt – Liomont (Mexico) – Cobra – Spharm	Catalent – Halls – JCR – mAbxience (Argentina) – ThermoFisher	BioKantai – CSL – Fiocruz (Brazil) – IDT – SII – Siam BioScience – SK Bioscience
Cansino Bio	AJ Pharma – DrugMax (Mexico) – Solution Biologics		
Gamaleya	R-Pharm – Panacea Biotech – Vabiotech – Houns Global – BIRMEX (Mexico) – Laboratorios Richmond (Argentina)	Virchow	Allum – GL Rapha – Gland Pharma – Karaganta PV – Uniao Quimica (Brazil)
Janssen	Aspen – Catalent – Grand River – Merck	Emergent – Merck	Reig Jofre – Sanofi
Moderna	Baxter – Catalent – Recipharm – Rovi – Sanofi – Samsung Biologics	Cordenpharma – Lonza	Takeda
Novavax	Baxter – Endo – GSK – Jubilant – Siegfried	ADG Biologics – Fujifilm – Zenda Polypeptide – SK Bioscience	Fujifilm – SII – Takeda
Pfizer BioNTech	Novartis – Sanofi – Siegfried – Allergopharma – Belpharm – Eurofarma (Brazil) – Biovac – Baxter – Fosun	CRODA – Dermapharm – Evonik – Merck – Polymun – Rentschler – Evelead – AGC Biologics	Dermapharm
Sinopharm	Incepta – Vacsera – Sinergium (Argentina)		Group 42
Sinovac	Instituto Butantan (Brazil) – Lekhim – Pharmaliaga – Vacsera		Biofarma

When considering the contributions of the vaccine developers and CMOs based in the LAC region to the manufacture of COVID-19 vaccines, total regional production capacity for licensed COVID-19 vaccines is ~683 million doses per year. Figure 12 provides a detailed breakdown of the COVID-19 vaccine production capacity based on individual manufacturer capacity and the production capacity available for each COVID-19 vaccine platform being manufactured in the region.

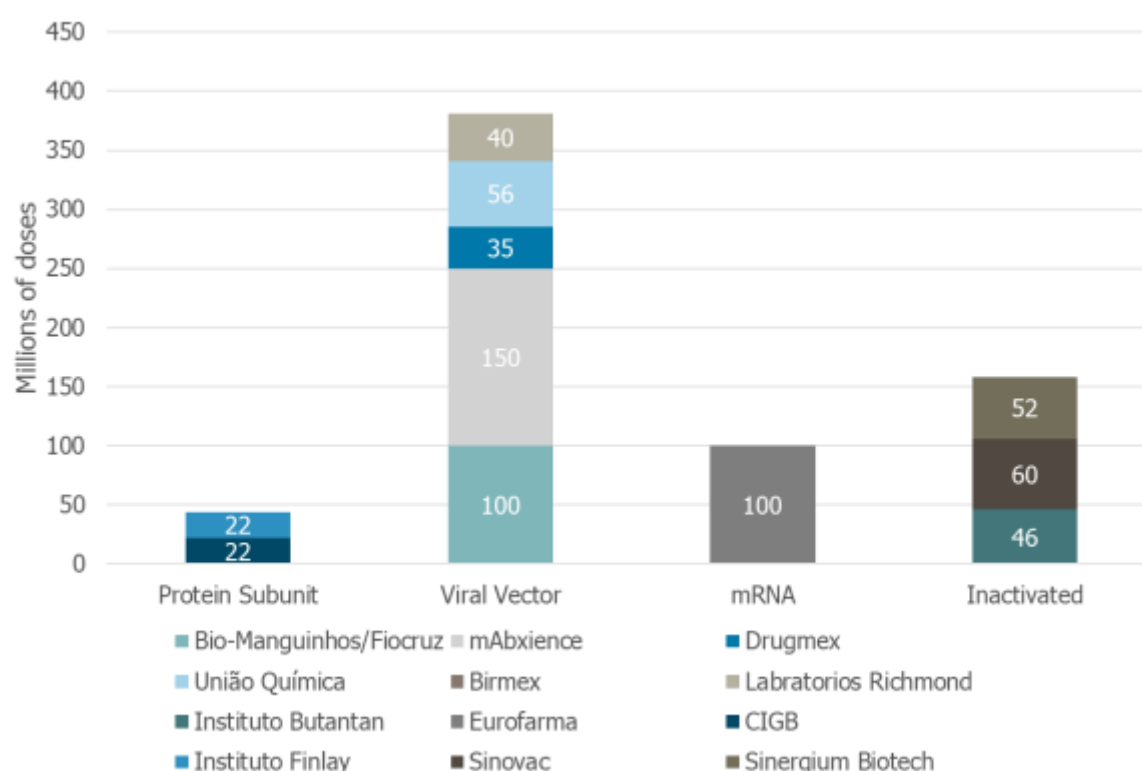
- The non-replicating viral vector vaccine platform is the largest in the region accounting for 56% (~381 million doses) of total COVID-19 vaccine production capacity. Recent studies seem to reverse the thinking that this type of vaccines cannot be used booster dose³⁷. Nonetheless, questions remain concerning the long-term suitability and attractiveness of this platform both as primary as well as a booster dose.
- The protein subunit vaccine platform is the one used by the 2 developers based in the LAC region; its production capacity is limited compared to other vaccine platforms and contribute only ~44 million doses or 6% of the estimated regional COVID-19 vaccine production capacity.
- Only 1 CMO supporting the fill and finish process of a mRNA COVID-19 vaccine is present in the region with no manufacturers currently producing drug substance for mRNA COVID-19, making the LAC region dependent on imported drug substance of mRNA vaccines. mRNA capacity is ~100 million doses or 15% of the estimated regional COVID-19 vaccine production capacity. Biomanguinhos-Fiocruz and Sinergium Biotech in collaboration with mAbxience have been selected to serve as manufacturing hubs for mRNA vaccines in the LAC region, which aim to negotiate technology transfers to support the development and production of mRNA COVID-19 vaccines (detailed further in subsequent section).

³⁷ R.L. Atmar et al. “Homologous and Heterologous Covid-19 Booster Vaccinations”, N Engl J Med, published on January 26, 2022, at NEJM.org, DOI: 10.1056/NEJMoa2116414

A.P.S. Munro et al., “Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial”, Lancet 2021; 398: 2258–76, [https://doi.org/10.1016/S0140-6736\(21\)02717-3](https://doi.org/10.1016/S0140-6736(21)02717-3)

- The inactivated COVID-19 vaccine platform as well has only the fill and finish processes being performed by CMOs in the region. This vaccine platform account for 23% of the total capacity (~158 million doses)

Figure 12: Total COVID-19 vaccine supply in LAC region, by vaccine manufacturer and vaccine technology platform (details on the different vaccine platforms in Annex 1)



While the LAC region has an existing, well-functioning vaccine manufacturing footprint producing COVID-19 vaccines, particularly those using the non-replicating viral vector platform, several key capability gaps exist that may still impact the regional preparedness and response to a pandemic. These gaps include:

1. Limited set of manufacturers with the capabilities to perform rapid, end-to-end vaccine development and commercialization in an emergency context, as evidenced by only 2 vaccine developers based in the region successfully developing in-house COVID-19 vaccines.
2. Very limited number of manufacturers in the region with the capacity to produce drug substance for COVID-19 vaccines. There are currently only 3 manufacturers based in PROSUR member states that are producing COVID-19 vaccine drug substance and all of them are based on the non-replicating viral vector platform technology. The utility of this manufacturing capacity may be limited if viral vector-based vaccines cannot be effectively used in COVID-19 vaccine booster programs or if the facilities cannot be repurposed to produce other new vaccines using the same platform technology.
3. No vaccine manufacturers in the region with the capabilities to produce drug substance of mRNA vaccines, a critical platform technology that has emerged to support rapid vaccine design in a pandemic environment. The success of the mRNA vaccine manufacturing hubs established in the region is critical to addressing this gap in manufacturing capability.

Global and regional initiatives to support vaccine development and manufacturing

There are several active regional initiatives in the LAC region and elsewhere which are aimed at supporting improved regional vaccine development and manufacturing self-sufficiency. This assessment details several of these key initiatives and identifies potential complementarities and misalignments for consideration as part of PROSUR's efforts to enhance future pandemic preparedness and regional vaccine manufacturing capabilities among member states.

CEPAL-CELAC

The United Nations Economic Commission for Latin America and the Caribbean (CEPAL) and Community of Latin American and Caribbean States (CELAC) have jointly performed an assessment of regional vaccine supply in the LAC region and have developed a corresponding plan to ensure future regional vaccine supply self-sufficiency. This plan has identified several critical areas for action (detailed below) which may be aligned with PROSUR goals and potential activities to improve vaccine self-sufficiency in the region:

1. Strengthening of regional pooled vaccine procurement mechanisms
2. Creation of regional markets via pooled procurement strategies
3. Formation of vaccine development and manufacturing consortiums
4. Development of regional clinical trial infrastructure
5. Securing access to key vaccine intellectual property
6. National medical regulatory agency strengthening and capacity building

CELAC and CEPAL have planned a series of workshops in late 2021 and early 2022 focusing on three initial areas: regulatory strengthening, establishment of a regional clinical trial platforms and vaccine procurement. Each of these areas is relevant for PROSUR and are highly complementary to PROSUR's vaccine self-sufficiency objectives. There is therefore an important opportunity for PROSUR collaboration with CEPAL, CELAC and other regional institutions and forums to achieve the collectively desired objectives regarding regional vaccine production.

PAHO mRNA vaccine manufacturing hubs

In the second part of 2021, PAHO announced that it would support the establishing of regional vaccine manufacturing hubs with a focus on the development of mRNA vaccines. Following the review of bids from interested pharmaceutical companies based in the LAC region, PAHO announced that two manufacturers in PROSUR member states were selected as the regional hubs:

Biomanguinhos-Fiocruz based in Brazil and Sinergium Biotech in collaboration with mAbxience, both based in Argentina. Together, these two vaccine manufacturers possess some of the most advanced manufacturing capabilities in the LAC region, as evidenced by their broad product portfolios (detailed in subsequent section). PAHO is now focused on convening a regional consortium to support technology transfer of mRNA vaccine technology to each of the manufacturers, to support the development and production of new mRNA vaccines for COVID-19.

The lack of regional capabilities to manufacture drug substance for COVID-19 vaccines based on the mRNA platform, as highlighted in the previous section of this assessment, is an important gap in the region's COVID-19 pandemic preparedness. By supporting key vaccine manufacturers in the region to develop the capabilities to develop and manufacture mRNA vaccines, the initiative directly benefits PROSUR countries that are host of the two selected manufactures. To ensure that the regional hubs are developed in a manner that guarantees support to all PROSUR countries and the broader LAC region, it will be critical to collaborate closely with PAHO in the definition of the goals of the initiative and its mode of operation. Specifically, there is an opportunity for PROSUR to help

PAHO to secure the necessary financing to support the development of both manufacturing hubs and negotiate access to the requisite technologies to facilitate mRNA vaccine development that can be supplied for the region.

Emerging areas of focus

After almost 2 years, areas of critical importance have emerged both for the response to the COVID-19 pandemic and for future pandemic preparedness.

To establish self-sufficiency, securing **access to critical know-how and intellectual property** related to COVID-19 vaccines and vaccine platforms will be essential. Access to specialised know-how and intellectual property can enable local manufacturers to internalize different components of the vaccine manufacturing process, and facilitate the development of novel or improved vaccines including by using platform technologies that allow for rapid vaccine design (e.g., mRNA)³⁸.

The global COVID-19 vaccination effort has also highlighted the importance of reliable access to vaccine manufacturing inputs including ingredients, components, equipment, containers, and packaging. The production of these inputs is dominated by a small number of manufacturers based in North America and Europe and **establishing capabilities to manufacturer key production inputs** can help to support improved vaccine supply security in the future.

Efforts are also underway in different regions to **support improved clinical trial networks**. These networks can be leveraged to support localised clinical development efforts that can facilitate tailored product design for the specific regional epidemiological needs as well as a smoother registration in the countries in the region as result of the generation of regional-specific data. Additionally, improved local clinical trial capacity has the potential to support regional manufacturers to evaluate their vaccine candidates more quickly through easier access to trial participants and streamlined data management.

Pooled procurement mechanisms are also increasingly viewed as key tools to the COVID-19 response and future pandemic preparedness. After initial challenges, the European Union has successfully contracted 4.2 billion doses of COVID-19 vaccines through 2023³⁹, for exclusive access by its member countries thereby providing the region with secure COVID-19 vaccine supply. As already proven successfully for routine vaccines by UNICEF Supply Division, PAHO Revolving Fund, the Baltics countries in Europe, leveraging larger pools of demand provide additional leverage in negotiation with key global or local vaccine manufacturers. Moving forward, these mechanisms should be used, also for vaccines for pandemic response secure more effective contracts than bilateral agreements between governments and manufacturers. These procurement mechanisms can also help to de-risk manufacturer development activities related to pandemic vaccines through advance purchase agreements or funding for specific development activities, which are linked to access to developed products. To foster an improved regional or subregional vaccine manufacturing ecosystem, these types of advance investments by pooled-procurement mechanisms may be required.

Lastly, many challenges emerged concerning the **regulatory** reviews and processes for COVID-19 vaccines in countries without domestic clinical developing capabilities and/or with national regulatory authorities of limited strength. Many of those countries did not have emergency use

³⁸ There are at least 5 different vaccine platforms being used for currently licensed COVID-19 vaccines: non-replicating viral vector, mRNA, protein subunit, inactivated, and DNA.

³⁹ https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en accessed on January 2022

authorization processes in place and while regulatory harmonization and reliance was used and resulted in some efficient authorizations in countries of use, shortcomings remained that resulted in delays and reduced access. Regulatory harmonization efforts can help to simplify the reviews manufacturers must undergo to achieve marketing authorisation, which are often different for each regulator. Something that can become critical during a health emergency to facilitate more streamlined vaccine development and supply access. Additionally, NRA oversight is critical to the success of manufacturing efforts. The overall limited numbers of NRAs with the appropriate level of maturity, in accordance with the WHO's Benchmarking Tool, represents a challenge everywhere including in the LAC region.

Regional development and manufacturing for routine vaccines

Methodology

A review of public information sources was performed to map existing vaccine developers and manufacturers based in the LAC region. Information sources included but were not limited to WHO's Market Information for Access to Vaccines initiative (MI4A)⁴⁰, PAHO⁴¹ and UNICEF Supply Division⁴² market reports and select journal publications. Information was consolidated for each vaccine manufacturer for all vaccine currently marketed and vaccines in the latter phase of clinical development (phase III). Contracts or licensing agreements with other pharmaceutical companies were analysed as well as available specific information for manufacturing capacity for licensed vaccines. PROSUR member states were also surveyed and provided inputs regarding domestic vaccine ecosystem, identifying local vaccine developers and manufacturing entities.

Differently from COVID-19 vaccine, the routine vaccines have well-established processes and a good understanding exist of those and of the market dynamics. Therefore, the focus has been more directed towards the estimate of the Available Supply for Commercialization (ASC)⁴³ for each manufacturer. A different, a more relevant metrics than the manufacturer's maximum production capacity; something that, for varied reasons, may never materialize hence shall mislead analyses and decisions stemming from them. This information was used to develop an estimation of the regional supply available within each of the vaccine markets.

Results

There are over 19 public and private entities which are currently manufacturing vaccines or have done so historically. The regional vaccine manufacturing base is primarily concentrated in Argentina, Brazil, and Cuba. Each country has multiple manufacturers capable of producing several different vaccines using a variety of vaccine platform technologies, including the inactivated, live attenuated, protein subunit and virus-like particle (VLP) platforms. Figure 13 provides more detail regarding the vaccine manufacturers based in LAC region. Annex 1 contains more detail on the required manufacturing processes for different types of vaccines.

Figure 13: Identified vaccine developers and manufacturers in the LAC region

⁴⁰ <https://www.who.int/teams/immunization-vaccines-and-biologicals/vaccine-access/mi4a/mi4a-market-studies>

⁴¹ <https://www.paho.org/en/revolvingfund>

⁴² <https://www.unicef.org/supply/vaccines>

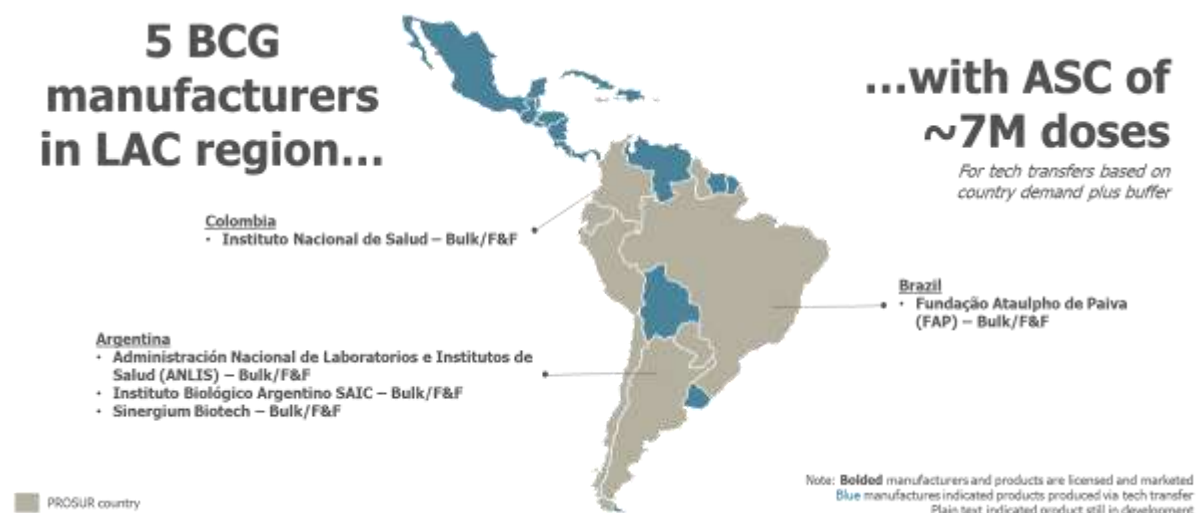
⁴³ As per WHO's MI4A initiative methodological approach, Available Supply for Commercialisation," is defined as "the number of doses available for sale at the global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events). This differs from the manufacturing capacity or the plant yearly throughput".



BCG Vaccine

There are 5 different manufacturers in the LAC region which produce BCG vaccine, among the 22 manufacturers producing the vaccine globally. Three of the manufacturers are in Argentina, while 1 manufacturer is located in Brazil and Colombia, respectively (Figure 14). Based on publicly available information, each of the manufacturers can perform the drug substance bulk production, along with the formulation, filling and finishing processes of the manufacturing process. Together, the 5 manufacturers have an estimated average supply for commercialization of ~7 million doses of BCG vaccine per year.

Figure 14: BCG vaccine manufacturers in the LAC region and aggregate ASC estimate



Pentavalent vaccine (DTP-containing)

There are 7 different manufacturers in the LAC region which produce DTP-containing vaccines, among the 45 manufacturers producing the many different combination of those vaccines globally. There are 2 manufacturers located in Brazil and Cuba, respectively, while there is 1 manufacturer located in Argentina, Mexico, and Venezuela (Figure 15). Currently, ANLIS and Instituto Finlay produce DTWP; Biomanguinhos, Instituto Butantan (the latter two are also collaborating to develop and produce a Pentavalent product) and Institute Rafael Rangel Caracas produce DTWP-Hib, while

CIGB is the only manufacturer currently producing a licensed DTwP-Hib-HepB (pentavalent) vaccine. Biomanguinhos is currently developing both pentavalent and hexavalent (pentavalent + IPV) vaccines. The DTP-containing vaccines produced in the region are not reliant on technology transfers from manufacturers outside the region and regional manufacturers can perform drug substance production processes. When combined, the 7 manufacturers have an estimated average supply for commercialization of ~83 million doses per year across all the different combinations of DTP-containing vaccines. The local production and supply of pentavalent vaccine is problematic in the LAC region with only CIGB producing a licensed product that is used for the domestic routine immunization program.

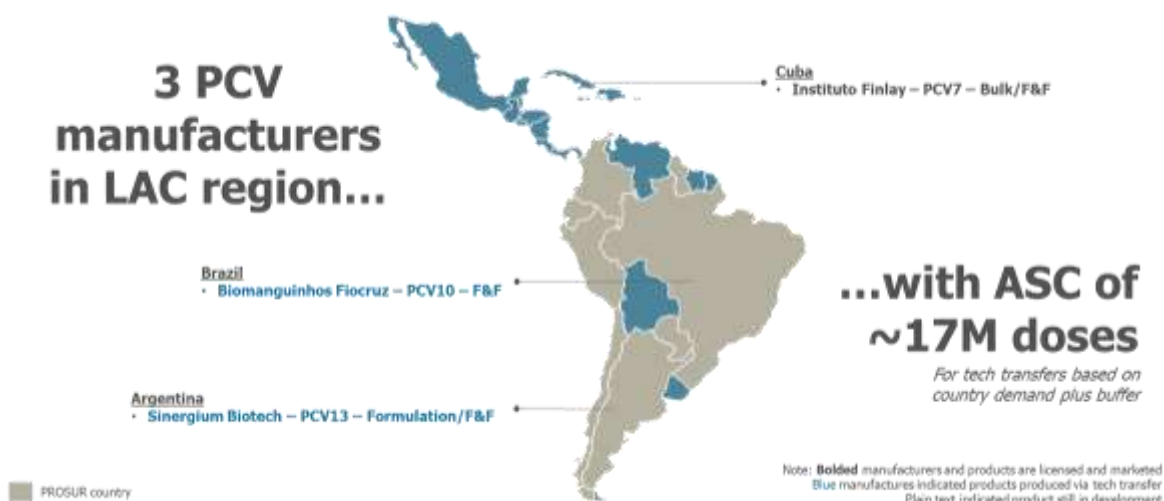
Figure 15: DTP-containing vaccine manufacturers in the LAC region and aggregate ASC estimate



Pneumococcal Conjugate Vaccine

There are 3 different manufacturers in the LAC region which produce PCV vaccine. Those are in Argentina, Brazil, and Cuba, respectively (Figure 16). Each of the manufacturers produces a different type of PCV vaccine. Instituto Finlay produces a locally developed PCV7, while Biomanguinhos and Sinergium Biotech have technology transfers in place with GSK and Pfizer to perform filling and finishing processes for PCV10 and PCV13, respectively. Therefore, Instituto Finlay is currently the only manufacturer in the LAC region who performs all processes of the PCV manufacturing process within its own facilities, one of 5 manufacturers globally with this capability. Together, the 3 manufacturers have an estimated average supply for commercialization of ~17 million doses of PCV vaccine per year.

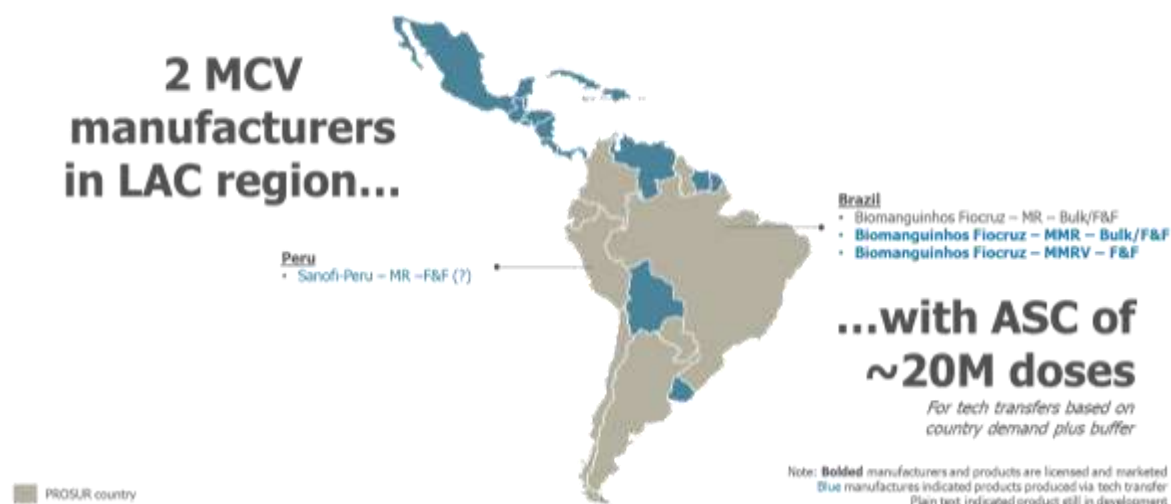
Figure 16: PCV vaccine manufacturers in the LAC region and aggregate ASC estimate



Measles Mumps Rubella (MMR) and Measles Mumps Rubella Varicella (MMR-V) vaccines

There is 1 manufacturer in the LAC region which produces MCV vaccine, among the 15 manufacturers producing MCV vaccines globally and one local distributor. This manufacturer, Biomanguinhos, is in Brazil (Figure 17). The manufacturer relies on technology transfers to produce different MCVs MR, MMR and MMR-V. The company also has a MR pipeline candidate which will reduce Brazil's reliance on technology transfers in the future. The 2 suppliers have an estimated average supply for commercialization of ~20 million doses per year across the different type of MCV vaccine. Access to this capacity by other countries in the region is constrained by limitations in commercial scope agreed to as part of the tech transfer

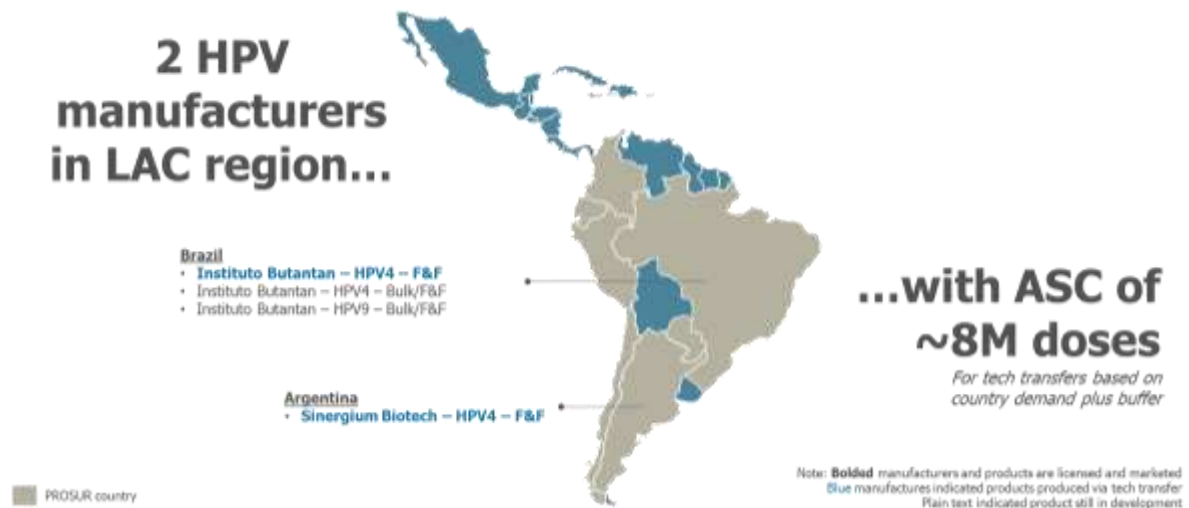
Figure 18: MCV vaccine manufacturers in the LAC region and aggregate ASC estimate



Human Papilloma Virus (HPV) vaccine

There are 2 different manufacturers in the LAC region which produce HPV vaccine, located in Argentina and Brazil, respectively (Figure 19). Both Instituto Butantan and Sinergium Biotech have technology transfers in-place to perform the filling and finishing processes for HPV4 drug substance produced outside the LAC region by 2 of the 3 manufacturers globally with end-to-end manufacturing capabilities of HPV vaccines. Instituto Butantan is currently working to fully localise HPV vaccine production. Between the two HPV suppliers, they possess an estimated average supply for commercialization of ~8 million doses of HPV vaccine per year.

Figure 19: HPV vaccine manufacturers in the LAC region and aggregate ASC estimate



Yellow Fever vaccine

There are 3 different manufacturers in the LAC region which produce yellow fever vaccine. Biomanguinhos in Brazil and Instituto Nacional de Salud in Colombia, both perform drug substance and formulation, filling and finishing processes for licensed vaccines, while ElieMechnikov, in Nicaragua, is currently developing a pipeline yellow fever vaccine candidate (Figure 20). The manufacturers based in Brazil and Colombia have an estimated average supply for commercialization of ~26 million doses of yellow fever vaccine per year.

Figure 20: YFV vaccine manufacturers in the LAC region and aggregate ASC estimate

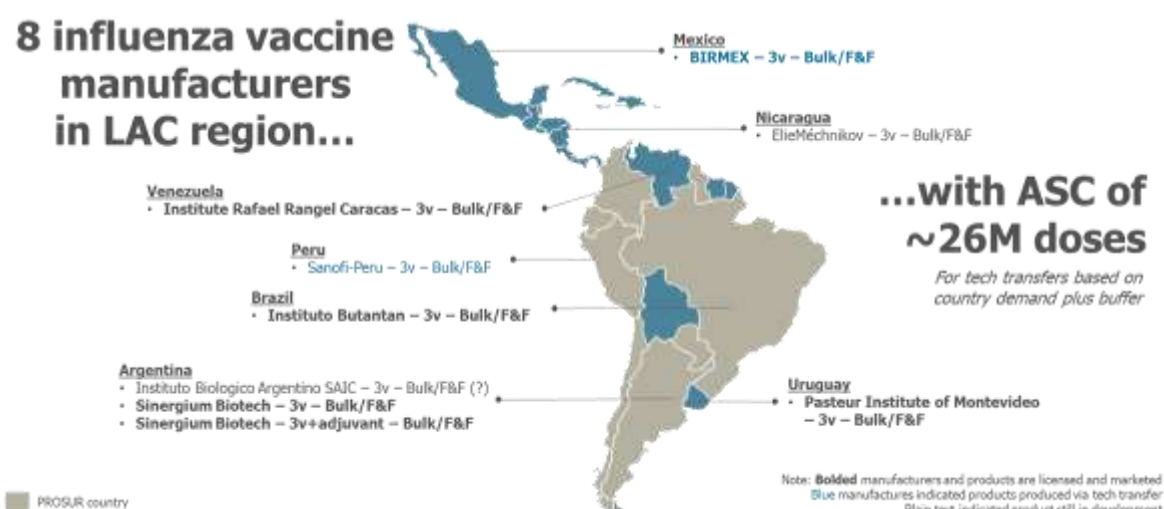


Seasonal influenza vaccine

There are 5 different manufacturers in the LAC region with existing or planned capabilities to perform manufacturing of drug substance and formulation, filling and finishing as well as 2 manufacturers with pipeline products and one national distributor (Figure 21). Manufacturers in the region currently manufacture trivalent influenza vaccines, and there are currently no local clinical development programs for quadrivalent influenza vaccines. The manufacturers in the region have a collective estimated average supply for commercialization of ~26 million doses of seasonal influenza vaccine per year. The existing seasonal influenza vaccine manufacturing base provides the region

with the foundational elements to rapidly design and produce a pandemic vaccine in the event of the emergence of a pandemic influenza strain.

Figure 21: Seasonal influenza vaccine manufacturers in the LAC region and aggregate ASC estimate

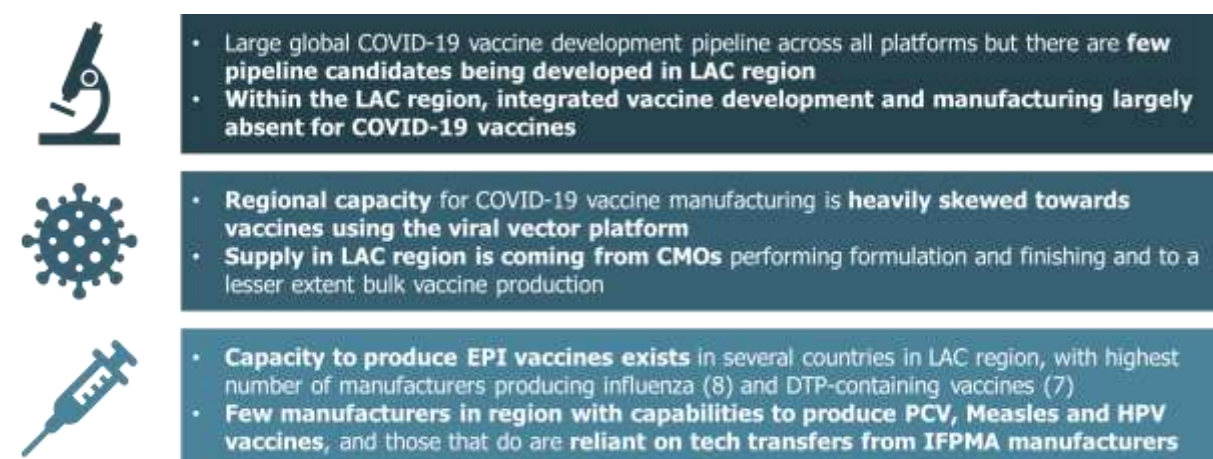


Summary of key findings

Following a review of the vaccine development and manufacturing ecosystem in the LAC region, several key findings have emerged regarding the region’s capabilities to develop and produce vaccines. The findings for both COVID-19 and routine vaccines are summarized below and in Figure 22:

- In the LAC region, there are **few COVID-19 vaccines which have been developed or are under development**, compared to other regions, and integrated clinical development and manufacturing of COVID-19 vaccines by manufacturers has been very limited.
- COVID-19 vaccines available in the LAC are **largely being supplied by CMOs** for vaccine suppliers outside the LAC region. Regional CMOs are performing drug substance and/or formulation, filling and finishing manufacturing processes for COVID-19 vaccines, with capabilities to produce up to ~683 million doses per year. The LAC region is therefore largely reliant on access to technology developed elsewhere to ensure supply of COVID-19 vaccines.
- The available COVID-19 vaccine supply is heavily skewed towards vaccines which employ **non-replicated viral vector platform technology**, with multiple CMOs producing these vaccines, with both bulk antigen and filling & finishing capabilities, the latter potentially being used for other platforms and other vaccines. Regional capabilities are instead more limited for mRNA COVID-19 vaccines, where manufacturing capabilities are limited to filling and finishing processes.
- There is a relatively **strong regional manufacturing base to produce vaccines for national immunization programs**, particularly in Argentina and Brazil.
- For other vaccines which are critical for national immunization programs, including PCV, MCV and HPV, there are few manufacturers in the region capable of developing and producing these vaccines, making the region reliant on technology transfers from IFPMA manufacturers based outside the region.

Figure 22: Key findings from LAC vaccine supply analysis



Supply-demand balance

The supply-demand balances identify the areas of self-sufficiencies and the dependencies that exist if a regional only perspective of supply is taken. The analysis of the balances also quantifies the gaps between vaccine supply and demand that should be addressed by new manufacturing capabilities if self-sufficiency goals are to be pursued.

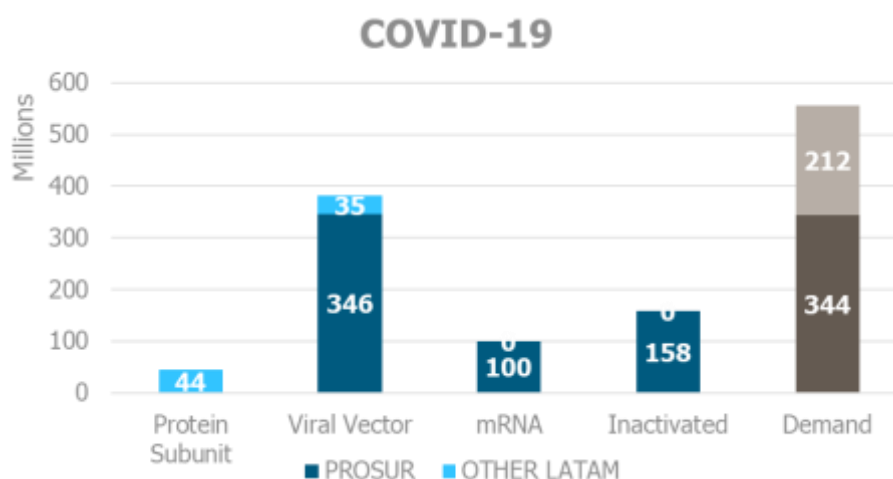
Following the estimation of the supply and demand for COVID-19 and other routine vaccines in the LAC region and PROSUR member states, the supply-demand balance in the LAC region and in PROSUR for each of the vaccine markets was evaluated to assess the condition of supply surplus or deficits for the LAC region and PROSUR. It should be noted that those balances provide only a preliminary view of the supply health of the region. Several factors impact the full access to the supply produced in the region:

- The available supply, while produced in LACs, can be contracted fully or partially with other regions. This is especially likely in the case of contracted manufacturing where the local CMO is not owning or possessing the commercialisation rights for the final product that it is processing on behalf of the originator.
- The available supply, when result of tech transfer, may have contractual limitation to its sharing outside the country of the recipient.
- Vaccines may not be registered in all countries; therefore, some countries may not have access to them.
- Countries may have strong preference for specific vaccine(s) and will not consider the entire portfolio as fully interchangeable.

For **COVID-19 vaccine**, the total LAC regional supply capacity or contracted supply is higher than the total demand with an excess supply of 167 million doses (Figure 23). The PROSUR excess is significantly higher, 300 million doses, in view of the concentration of production capacity in the PROSUR countries. No single platform can serve the entire LAC region, but PROSUR countries can all be served by non-replicating viral vector vaccines produced in the sub-region. The viability of non-replicating Viral Vector vaccines supply to serve the booster needs of the region is dependent on the evolving science and policy recommendations. In the event that viral vector vaccines cannot be used for booster doses, the current regional capacity will not be sufficient to serve demand in PROSUR and the broader LAC region. In any case, it should be reiterated that this capacity is not accessible

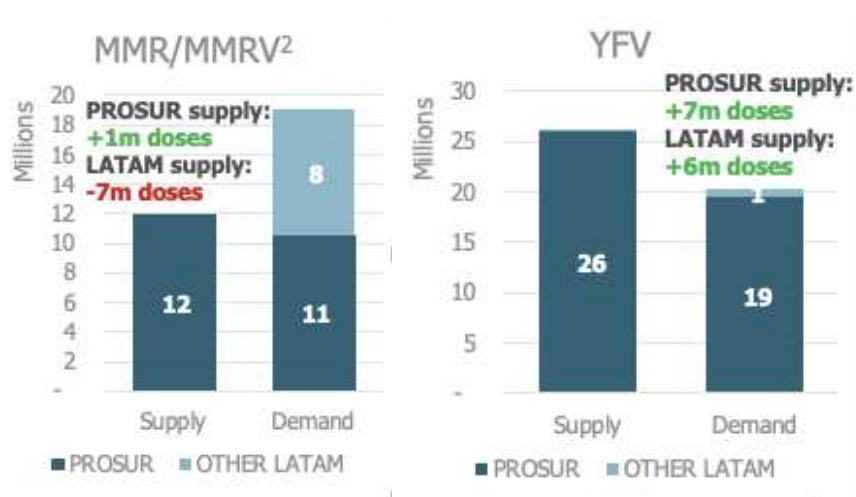
under the current circumstances, being resulting primarily from CMOs that provide their capacity to third parties located outside the region.

Figure 23: Estimated vaccine supply and demand in LAC and PROSUR for COVID-19 vaccines (demand includes exclusively future booster needs)



The other regional vaccine markets where PROSUR is estimated to have surplus vaccine supply are MCV and YFV (Figure 24). In both cases PROSUR as subregion has a theoretical surplus while the rest of the countries in the LAC region lack access to locally produced MCV (MMR and MMRV). The surplus for MCV in PROSUR is dependent on renegotiation and expansion of commercialization rights to vaccines currently produced in Brazil. The relevance of YFV access is limited for non-PROSUR countries that do not experience endemic yellow fever.

Figure 24: Estimated vaccine supply and demand in LAC and PROSUR for MCV and YFV



For the remaining vaccine markets including BCG, HPV, PCV, and Pentavalent/Hexavalent, there is an estimated deficit in vaccine supply due to a combination of a lack of capable manufacturers, commercialization rights or production capacity (Figure 25). Vaccine supply deficits are greatest in the PCV and Pentavalent markets, as PCV suppliers in the region are focused on domestic markets based on tech transfer agreements, and there are currently no pentavalent producers in the LAC region outside of Cuba.

Figure 25: Estimated vaccine supply and demand in LAC and PROSUR for BCG, Pentavalent/Hexavalent, PCV and HPV



Overall, the regional supply-demand balance for vaccines in LAC is negative, as available vaccine produced in the region, even under less restrictive conditions, are insufficient to meet regional or subregional demand, except for COVID-19 vaccines. This contrasts with the estimated global supply-demand balances for the same vaccines, in which most markets are in a healthy state except for HPV vaccine (Figure 26).

Figure 26: Global, LAC region and PROSUR supply-demand balances

Vaccine	Global balance (mid-term)	LAC regional balance	PROSUR balance
COVID-19	Green	?	?
BCG	Green	Red	Red
Pentavalent/Hexavalent	Green	Red	Red
PCV	Green	Red	Red
Measles	Green	Red	?
HPV	Yellow	Red	Red
Yellow Fever	Yellow	Green	Green

Legend: green = supply > demand + 10%; yellow = demand + 10% > supply > demand; red = supply < demand

If relying solely on supply from local vaccine developers and manufacturers, none of the vaccine markets in the LAC region or PROSUR would be considered healthy at this time except for Yellow

Fever. The MCV market is balanced only when considering the full flexibility of the supply; as this supply is current inflexible, the estimated balance is hypothetical. The LAC region countries are dependent on suppliers from other regions to fulfil their demand. If the focus is limited to the PROSUR countries, these countries are slightly better positioned to address their vaccine supply needs because of the strong vaccine manufacturing bases in Argentina and Brazil, though subregional access to vaccines like HPV, MCV and PCV are conditioned on the commercial agreements linked to existing technology transfers.

Country attractiveness to be receipt of vaccine technology transfers

Based on the output of the supply-demand balance analysis, access to necessary technology is essential for the establishment of the vaccine manufacturing capacity needed to fill the supply gaps in PROSUR and the LAC region. This access can be achieved through two possible strategic approaches: (a) the organic development of local manufacturing through the hiring of experienced technical staff and large investments in the development of local know how and skills, which carries very high costs and a high risk of failure; or (b) the transfer of technology from an originator which is willing to partner to allow the localisation of its technology. The latter approach is fully conditional on the will of the technology originator and under certain conditions (primarily the know-how of the technology recipient) can be significantly less risky. However, the licensor can limit the impact of technology transfers on access by the limiting the commercialization rights to certain countries or the scope to filling and finishing preventing upstream move to drug substance production.

A study performed by the International Federation of Pharmaceuticals Manufacturers Associations (IFPMA)⁴⁴ identified eight factors which are evaluated by originators and owners of technology which inform decisions about the licensing of proprietary technology to outside firms. The framework provides a straightforward way of assessing country readiness to accessing technology from an originator; the more conditions are met the more likely it is that, subject to the existence of a suitable potential recipient of the technology, a country can be considered by originators as a favourable environment for technology transfers.

The eight areas, summarised in Figure 27, are described below:

- A domestic and a regional market for the technology in scope that is viable in size (sufficiently large), price levels (sufficiently high and stable) and reliability of the payors
- A political situation considered sufficiently stable not to represent a significant risk that changes in government will alter the rules and laws that regulate the vaccine business
- An economic and legal governance framework that is transparent and stable providing a predictable business environment in which to operate
- A functioning capital market that provides healthy and multiple opportunities for financing operations and new investments without having to rely exclusively on the banking sector or on public grants
- A policy and legislative context that protects and incentivize innovations. Irrespective of the real impact on the specific vaccine manufacturing area, the protection of intellectual propriety is seen by pharmaceutical companies a fundamental factor to protect their investments

⁴⁴ IFPMA, Technology transfer: a collaborative approach to improve global health - Published on: 25 January 2015 - <https://www.ifpma.org/resource-centre/ifpma-technology-transfer-a-collaborative-approach-to-improve-global-health/> - accessed on January 2022

- The proper access to demand and market information that can inform decisions of originators and recipients
- A regulatory system that adheres to the international standards (e.g., that has achieved at least a maturity level 3 as per the WHO Benchmarking Tool⁴⁵) which can ensure oversight of manufacturing activities and timely, reliable processes for achievement of marketing authorisation of new products or post-marketing changes for existing products
- The availability of skilled technical and management professionals that ensure recipient companies can locally source its workforce. This aspect is especially important for vaccines due to the complex processes required to produce vaccines at-scale, and the integrity of repeatable manufacturing processes being a core component of vaccine marketing authorisation. Skilled professionals in vaccine manufacturing are a very scarce resource.
- Clarity of economic development priorities with a focus on the health and biotechnology sectors which provide local producers with a supportive ecosystem for financing and procurement as well as a diverse and effective supplier base for equipment, production input and other materials required in the vaccine production processes.

Figure 27: IFMPA factors considered for technology transfers



Methodology

Based the IFMPA framework, meaningful indicators have been identified to measure the different influencing factors and for which reliable and complete data sources existed. For some of the influencing factors multiple indicators have been referenced to capture more comprehensively the different dimensions covered by each indicator. Figure 28 provides a summary of the selected indicators and data sources, which are detailed below.

Figure 28: Indicators to measure country attractiveness for technology transfers

⁴⁵ WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems - <https://www.who.int/tools/global-benchmarking-tools> - accessed on January 2022

Influencing Factor	Indicator	Source
Viable accessible local...	<i>Birth cohort x average price for Penta, PVC & RV</i>	OWD ¹ , MMGH ⁶
... and regional market	<i>Inclusion in Regional Cooperation Agreements</i>	WTO ⁵
Political stability ...	<i>Government Effectiveness</i>	World Bank ²
... and transparent economic governance	<i>Regulatory Quality</i>	World Bank ²
Appropriate capital market	<i>Market Capitalisation</i>	WEF ³
Innovation friendly environment ...	<i>Innovation ecosystem</i>	WEF ³
... with sound IP rights	<i>Intellectual Property Protection</i>	WEF ³
Proper access to information	<i>Transparency</i>	WEF ³
Adherence to high regulatory standards, including target facility GMP level	<i>NRA maturity level</i>	WHO ⁴
Skilled workforce: technical and management	<i>Skills of Future Workforce</i>	WEF ³
Clear economic development priorities	<i>Government long-term vision</i>	WEF ³

1: 2019 Revision of World Population Prospects – via One World in Data -

<https://ourworldindata.org/grapher/annual-number-of-births-by-world-region>

2: The Worldwide Governance Indicators (WGI) - <http://info.worldbank.org/governance/wgi/>

3: The Global Competitiveness Report 2019 -

<http://reports.weforum.org/global-competitiveness-report-2019/>

4: WHO-Listed Authority (WLA) - <https://www.who.int/initiatives/who-listed-authority-reg-authorities>

5: WTO: country participation in Regional Trade Agreements -

https://www.wto.org/english/tratop_e/region_e/rta_participation_map_e.htm

6: Desk reviews

- Attractiveness of the local market has been measured calculating the total market value in USD by examining the different price levels (Gavi, LMICs self-procuring, UMICs self-procuring and HICs self-procuring) of 3 key NIP vaccines (Pentavalent, PCV and RV) as monitored by WHO and the relevant target population, as measured by the UNDP (via One World in Data)
- Access to regional markets has been measured by the number of regional cooperation agreements each country is participating, as monitored by the World Trade Organization (WTO).
- Political stability has been measured using the Government Effectiveness indicator from the World Bank's Worldwide Governance Indicators (WGI) which reflects perceptions of the quality of public services, the quality of the civil service and the degree of its independence from political pressures, the quality of policy formulation and implementation, and the credibility of the government's commitment to such policies.
- Transparent economic governance has been measured using the Regulatory Quality Indicator from the World Bank's Worldwide Governance Indicators (WGI) that reflects perceptions of the ability of the government to formulate and implement sound policies and regulations that permit and promote private sector development.
- Appropriateness of the capital market has been measured using the total Market Capitalisation (in USD) from the World Competitiveness Report produced by the World Economic Forum that indicates the level of development of the local capital market.
- Friendliness of the economic environment towards innovation has been measured using the Innovation Ecosystem indicator from the World Competitiveness Report produced by the World Economic Forum that captures the business dynamism (administrative requirements and entrepreneurial culture) and the innovation capabilities (diversity and collaboration, research and development and commercialization).

- Protection of intellectual property has been measured using the Intellectual Property Protection Indicator from the World Competitiveness Report produced by the World Economic Forum.
- Proper access to information has been measured using the Transparency sub-pillar from the World Competitiveness Report produced by the World Economic Forum.
- Adherence to high regulatory standard has been measured using the WHO Benchmarking tool that produces a composite evaluation of National Regulatory Authorities by looking at 9 different essential functions. Additionally, the ability of NRAs to act as reference regional authorities for the Pan American Health Organization (PAHO) has also been considered. It is worth highlighting that the achievement of at least maturity level 3 on the WHO Benchmark rating is generally a precondition for being considered as a suitable target for tech transfer by any established technology originator. See Figure 29 for the NRA status in PROSUR countries.

Figure 29: Capacity of National Regulatory Authorities in PROSUR



An NRA is considered in condition to regulate WHO prequalification when has reached Maturity Level 3 along the scale of WHO's Benchmarking Tool. NRAs are appointed by PAHO as reference authorities when they have been assessed against PAHO standardized evaluation procedure and PAHO data collection tool

- Availability of skilled technical and management workforce has been measured using the Skills of Future Workforce sub-sub pillar from the World Competitiveness Report produced by the World Economic Forum that provides an overview on the likely development of the workforce based on two areas: critical thinking in teaching and pupil to teacher ratio in primary education.
- The clarity in economic development priorities has been measured using the Government Long-term Vision indicator from the World Competitiveness Report produced by the World Economic Forum based on the result of a survey.

For each of the 11 indicators, countries have been ordered based on the values recorded from the various sources. For all indicators except regulatory strength, the first 8 countries of the 23 have

been attributed a score of 3, countries from position 9 to position 16 a score of 2 and the last 7 countries a score of 1. For the regulatory strength, countries regulating WHO prequalification have been given a score of 3, countries acting as regional reference NRA have been given a score of 2, all other countries have been given a score of 1. The consolidated score (maximum 33, minimum 11) has been used to assess country attractiveness.

Results

Overall, countries clustered in high, medium, and low performing consistently across the various indicators. Chile and Colombia scored the highest with maximum scores across all indicators (except for NRA). Panama, Mexico and Argentina and Costa Rica subsequently scored the highest which were followed by Uruguay, Brazil, and Peru. PROSUR countries generally scoring among the highest of all countries 5 countries among the top 9 highest scoring countries (Figure 30).

Among the top scoring countries, Panama, Costa Rica, Uruguay, and Peru do not have fully functioning NRAs. Irrespective of their score in other categories, these countries will have to ensure achievement of a maturity level 3 on the WHO Benchmarking scale before being consider as a viable location for tech transfer by originators. is the need to strengthen NRA capacity is common across all countries in the region except Brazil.

The countries whose manufacturers have historically received tech transfer, which include Argentina and Brazil, score among the highest of all countries. The size of the Brazilian market has played a vital role in past tech transfer decisions.

Figure 30: Summary of the scoring across all indicators

COUNTRY	Market Value	Inclusion in Regional Trade Agreements	Government Effectiveness	Regulatory Quality	Market Capitalisation	Innovation ecosystem	Intellectual Property Protection	Transparency	NRA maturity level	Skills of Future Workforce	Government longterm vision	Total performance
Chile	3	3	3	3	3	3	3	3	2	3	3	32
Colombia	3	3	3	3	3	3	2	3	2	3	3	31
Panama	2	3	3	3	3	3	3	3	1	2	3	29
Mexico	3	3	3	3	3	3	3	2	2	2	2	29
Argentina	3	2	3	1	2	3	3	3	2	3	3	28
Costa Rica	1	3	3	3	2	3	3	3	1	3	3	28
Uruguay	2	2	3	3	1	3	3	3	1	3	3	27
Brazil	3	2	2	2	3	3	2	2	3	2	2	26
Peru	3	3	2	3	3	2	2	2	1	3	2	26
Dominican Republic	1	1	2	3	3	2	3	2	1	3	3	24
Honduras	1	3	1	2	1	2	3	2	1	2	3	21
Ecuador	2	2	2	1	2	2	2	2	1	2	2	20
Paraguay	3	2	2	2	2	2	1	2	1	1	2	20
El Salvador	1	3	2	2	3	2	1	2	1	1	1	19
Bolivia	3	1	1	1	2	1	1	2	1	2	2	17
Guatemala	2	2	1	2	1	2	2	1	1	2	1	17
Nicaragua	1	2	1	1	2	2	2	1	1	1	2	16
Venezuela	2	1	1	1	2	1	1	1	1	3	1	15
Cuba	2	1	3	1	1	1	1	1	2	1	1	15
Guyana	1	1	2	2	1	1	1	1	1	1	1	13
Belize	1	1	1	2	1	1	1	1	1	1	1	12
Haiti	2	1	1	1	1	1	1	1	1	1	1	12
Suriname	1	1	1	1	1	1	1	1	1	1	1	11

Conclusions and recommendations for prefeasibility assessment

Vaccine platform technologies

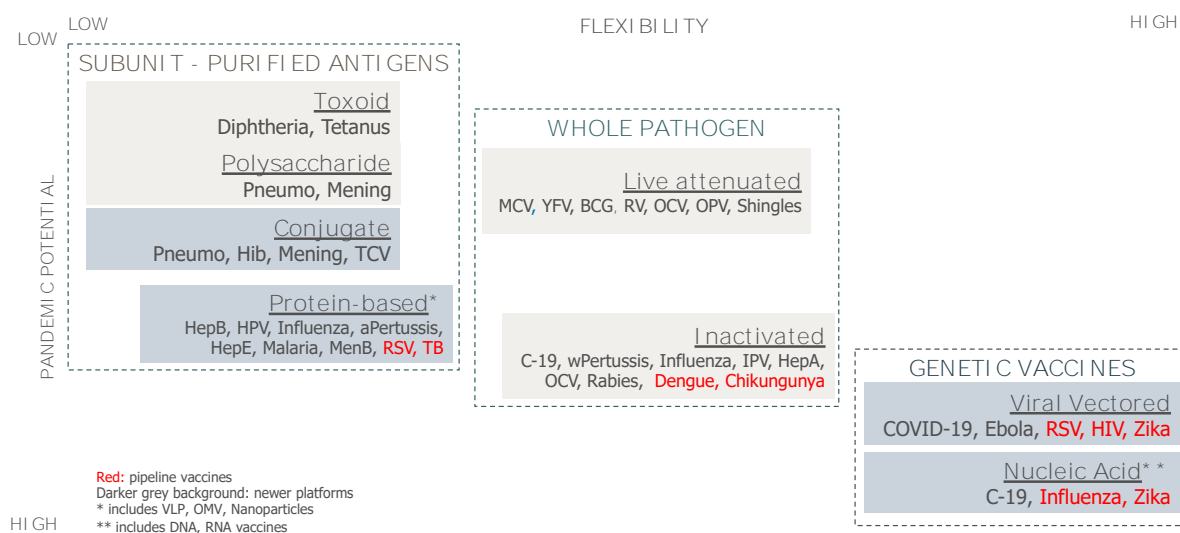
Vaccines used by NIPs in routine immunization programs as well as COVID-19 vaccines have different characteristics and use different technologies. The technologies used have implications on the design of a given vaccine, the required inputs, and the manufacturing methods to produce a finished vaccine product for use.

As described in Figure 31, seven main platforms are used in the production of vaccines, each of them with some variation and overlap:

- Toxoid vaccines (e.g., diphtheria and tetanus vaccines) which use a toxin (harmful product) made by the pathogen that causes a disease.
- Inactivated vaccines (e.g., COVID-19, whole cell Pertussis, Dengue, Chikungunya, Influenza, IPV) which use a killed version of the pathogen that causes a disease.
- Live attenuated vaccines (e.g., MCV, yellow fever, BCG, rotavirus and OPV vaccines) which use a weakened (or attenuated) form of the pathogen that causes a disease.
- Virus like particle vaccines (e.g., HPV vaccines) which uses molecules that closely resemble viruses but are non-infectious because they contain no viral genetic material.
- Subunit protein platform (e.g., COVID-19, acellular pertussis, hepatitis B, RSV, and tuberculosis vaccines) which use the antigenic parts of the pathogen (e.g., its protein, sugar, or capsid).
 - Conjugate vaccines are a specific type of subunit protein vaccines (e.g., PCV, TCV, Hib vaccines)
- Viral vector vaccines, including replicating and non-replicating (e.g., COVID-19, Ebola, RSV, HIV vaccines) which uses a modified version of a virus (not the pathogen in scope) to present a pathogen's protein to the immune system.
- Nucleic acid vaccines, including mRNA and DNA (e.g., COVID-19 vaccines) which use the cell machinery to make the proteins that trigger an immune response.

Figure 31: Vaccine platforms for routine and epidemic vaccines⁴⁶

⁴⁶ Within the LAC region, bolded products are licensed, products in blue text are produced via tech transfer, products in brown text are produced via CMO, products in red text are pipeline vaccines, products in plain and italicized text were not analyzed.



Among the existing platform technologies used to manufacture vaccines, the toxoid, live attenuated as well as the polysaccharide and conjugate subunit platforms have been primarily used for vaccines used by NIPs within routine immunization programs. The inactivated and protein-based subunit platforms have historically been used for both routine and epidemic vaccines, including COVID-19, Influenza, and pipeline vaccines of regional importance (e.g., Dengue and Chikungunya). To-date, the mRNA and viral vector platforms have only been used for epidemic vaccines, though vaccine developers are already testing pipeline vaccines candidate against other diseases using these technologies which may be used in routine immunization programs in the future.

By developing the capabilities to manufacture a vaccine using a specific vaccine platform technology, a manufacturer will have less difficulties in developing and producing other vaccines designed using the same platform, leveraging existing expertise and infrastructure. Vaccine platform technologies should therefore play a critical role in the determining PROSUR's strategy to securing the supply of different vaccines, based on existing and desired manufacturing capacities within the region.

The vaccine platform characteristics, the market conditions and PROSUR goals for vaccine supply within the subregion (i.e., self-sufficiency for specific routine vaccines, future pandemic preparedness) will have considerable influence and impact on the selection of the platform technologies and vaccines that vaccine manufacturers in the region pursue for local development or manufacturing.

Strategic Approaches to ensuring access to regional vaccine supply

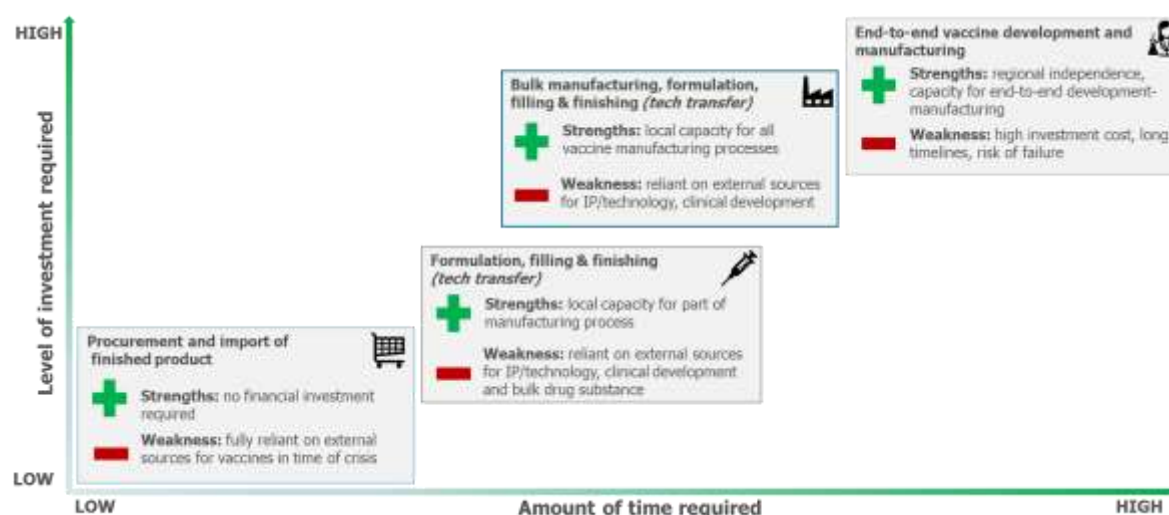
A range of potential approaches can be conceived to realize PROSUR's ambition of creating a self-sufficient vaccine ecosystem with the goal of securing reliable access to vaccines for COVID-19, vaccines against future pandemics and vaccines to serve the NIPs. As highlighted in earlier sections of this analysis, the development and manufacture of vaccines is a long-term, high-risk effort which requires substantial capital investment and technical expertise; furthermore, several pre-conditions need to be met both at national and individual manufacturing levels. The requirements can greatly vary based on the characteristics of the vaccine (or vaccines) targeted. It is therefore important to evaluate the alternative approaches to achieving self-sufficient vaccine supply, balancing the time and resources required to achieve local manufacturing capacity for the target vaccines with the economics and dynamics of the global market for those vaccines.

This analysis reviews the technical and market aspects and alternative strategies are described by examining PROSUR countries as operating in a concerted and integrated fashion, as if acting as a

single entity. The governance and legislative aspects that such setup may require are covered in the parallel governance analysis.

As detailed in Figure 32, four potential approaches can be pursued, each with unique time and resources required. Each approach can be applied independently for an individual vaccine allowing for a modular approach across a larger portfolio of products.

Figure 32: Manufacturing and procurement approaches to access vaccines



In a growing sequence of complexity and investment requirements those approaches include:

1. The simplest access strategy does not include development of domestic manufacturing capacity. Depending on the market health of each vaccine, PROSUR may decide to rely on the existing global vaccine manufacturing base and **pool procure to import finished vaccines from manufacturers already producing** the required vaccine(s). This is the approach currently in place for many countries via the PAHO Revolving Fund. For routine vaccines, the larger the volume of vaccines procured, the more positive impact can be achieved in terms of price and security of supply. Importantly, appropriate contractual terms need to be negotiated to ensure unlimited access to the necessary quantities under all circumstances. The overall financial implications of this approach are the most limited, for pandemic vaccines higher prices will need to be accounted for as result of the procurement guarantees that will need to be paid to guarantee priority access also in the event of a health emergency. In both cases, while contracting arrangements may improve the security of access, those will not reduce dependencies since they will not lead to strengthening of local vaccine manufacturing capacity. This approach will require focus on further strengthening regional/subregional procurement mechanisms, ensuring they have adequate financing to negotiate with vaccine manufacturers during health emergencies while also avoiding competing subregional procurement efforts. The key risks are: (a) in crisis situations (pandemic, outbreaks) vaccine nationalism can limit access or the market may become supply-constrained; (b) vaccines specifically addressing regional needs may not be developed; (c) market dynamics can change and markets once in healthy state may become constrained as result of market exits or changes in manufacturer production output.

This strategy may be appropriate for vaccine markets in a healthy state with differentiated manufacturer bases and with comparable products (e.g., BCG, Pentavalent). Furthermore, this strategy can be considered for vaccines whose platform are less represented in the portfolio of relevant vaccines for the region and whose business case will be less sustainable for a tech transfer. On the other hand, the strategy carries an inherent risk for vaccines required for prevention of pandemic/epidemic and outbreak response (e.g., Influenza, Measles, Yellow Fever) because of the way outbreaks and pandemic event distort normal vaccine market dynamics as result of supply shortages, vaccine nationalism, supply chain constraints.

2. The base access strategy involving establishment of manufacturing capacity can be limited in scope with local manufacturers performing only the **formulation, filling and finishing part of the manufacturing process**, with bulk drug product imported from manufacturers outside the region. **Those agreement need to be coupled with the negotiation of full commercialization rights for the vaccines, at minimum in PROSUR countries.** This is the approach adopted by some manufacturers in the region for HPV and PCV vaccines, even if with a limited geographical scope (Brazil). This strategy would enable PROSUR to establish or strengthen some elements of the vaccine manufacturing process, partially reducing the level of dependency from entities external to the region. Multiple technology transfers will be required across various technology platforms for the different vaccines in scope the region. Adequate regulatory capabilities from the technology recipient will be required to ensure that the new vaccines, including product and process, can achieve domestic and regional marketing authorisation. The NRA of the countries where the recipient is located will have also to show sufficient maturity (i.e., at least level 3 on the WHO benchmarking tool scale). This will require important efforts in NRA strengthening. Similar to the first strategy, the total volume in scope is a very important factor both for the economics of the operations as well as for the attractiveness of the value proposition for the technology originators. The strategy will require the availability of regulatory and clinical development capabilities as the new vaccines and the processes under which they are produced will need to receive new marketing authorisation from the local NRA. This approach requires a smaller level of investment compared to those seeking to establish capabilities for the entire manufacturing process or integration of the R&D component. It can also leverage the existing large base of CMOs existing in the region. The track record and experience of the originator is critically important because of the complete dependence of this strategy on the availability of vaccine bulk from the originator. The main risks linked to this approach are similar to those indicated for the procurement on the open market approach but partially reduced by the existence of contractual relationship regulating the access to the work-in-progress products.

This strategy may be appropriate for vaccines where formulation fill & finish is a general bottleneck, in which originators may be more interested in contract manufacturing partners or where competition is growing and players aim at locking markets from newcomers (e.g., HPV or COVID-19 after the initial phase). Technology transfers for existing platforms or platforms that can share the downstream processes (from this perspective live or live attenuated vaccines and high biosecurity level products require separate facilities and processes) are most appropriate. This strategy, as indicated for the open market approach, carries an inherent risk for vaccines required for prevention of pandemic/epidemic and outbreaks, considering their potential to limit the access to vaccine bulk were this to become a constraint.

3. A more comprehensive strategy aimed at equipping the region with full manufacturing capacity involves the negotiation of technology transfers involving the full manufacturing process from **bulk manufacturing to formulation, filling and finishing** with full commercialization rights for the produced vaccines, at a minimum in PROSUR countries. This approach would enable local manufacturers to develop capacity to perform all parts of manufacturing and would require important levels of investment for facilities and time required to transfer technology and build local expertise. This strategy will allow full control of the manufacturing process eliminating any dependencies from activities outside the region except for the access to the input ingredients and consumables required to produce vaccines, components which have proven problematic in the early phases of the production of COVID-19 vaccine. Similarly but to a larger extent than the prior strategy, availability of strong regulatory **and clinical development capabilities will be paramount**. As indicated for the fill and finish strategy, the NRA of the country of the recipient will need to show adequate level of maturity. The absence of research capabilities will leave the technology recipient, and thereby the region, dependent on technology originators to perform the prioritisation of the vaccines and their characteristics for development. The local manufacturers will have to demonstrate their track record in vaccine production to be credible to technology originators (i.e., pharmaceutical or biotechnology companies) to be able to access the technology for local use.

This strategy may be appropriate for vaccine or technology platforms that are key commercial drivers of technology originator strategies, for which companies could be reluctant to share to full technological knowledge and expertise (e.g., PCV 13 or mRNA COVID-19 for Pfizer, HPV 9 for Merck, Quadrivalent Influenza or acellular Pertussis Hexavalent for Sanofi-Pasteur). Vaccine platforms with broad reach in the number of products they can support would be especially appropriate, thereby allowing a larger return on the initial investment and a fuller exploitation of the developed expertise. From an economic standpoint, higher price vaccines (as the ones mentioned above) will be more suitable for technology transfer and local manufacturers as they will support a more sustainable business model. This approach is likely resulting in higher prices for the vaccines in scope since economies of scale and process efficiencies normally takes a long time to materialise.

4. Establishment of **end-to-end vaccine development and manufacturing** capabilities for a specific vaccine or group of vaccines is the most comprehensive approach to achieve regional supply objectives. Realistically, this strategy will need to focus on few selected vaccine platforms which are relevant to serve regional vaccine demand (only a handful of manufacturers – GSK, Sanofi and Serum Institute of India – have developed over a very long period of time the capability of successfully handling multiple platforms). With this strategy, PROSUR countries would be able to achieve full regional self-sufficiency, reducing dependencies from entities outside the region. Once fully implemented, the strategy will allow PROSUR countries to select priority vaccines, design and develop them according to region's specific epidemiological needs, manufacture them in the necessary quantities to fulfil regional needs and distribute them to all countries in the region. While the most effective strategy from an access standpoint, this approach represents the most capital and time intensive strategy. The most important risks are: (a) sufficient financial resources may not remain available in the long run; (b) the inherent clinical development risk that vaccines

targeted for development fail during their clinical trials and never reach regulatory approval and commercialization. Given the extended time required to implement and build capacity among local manufacturers, a gradual approach will most likely be required that starts from less integrated strategies and progressively builds capacity to integrate upstream development and manufacturing processes. This will also require renegotiation of existing tech transfer agreements which use externally licensed IP to supply select countries in the region to be extended for supply to become available to all PROSUR countries.

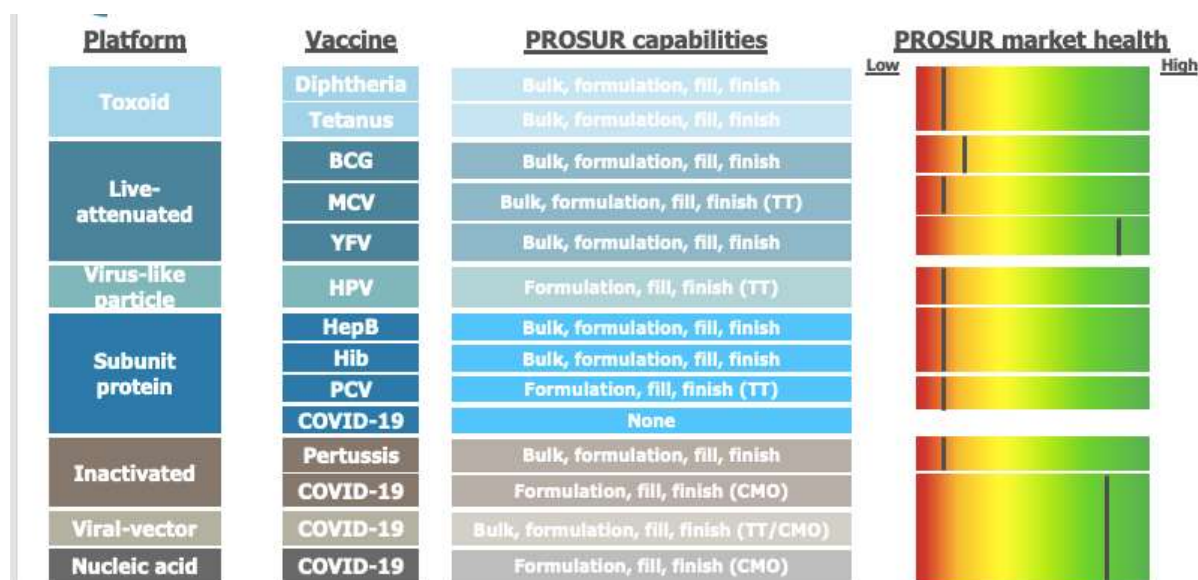
In the short-term, this strategy may be pursued for simpler vaccine platforms (e.g., mRNA, Inactivated), where the expertise and technologies can be acquired and developed faster. In parallel, partnerships can be sought with Product Development Partnerships (PDPs) to advance on more complex technologies and help capacity building efforts. The approach is relevant for both novel vaccines where local development and end-to-end manufacturing are to be established (e.g., as well Nucleic Acid vaccines) as for new and improved versions of vaccines which are currently produced locally where upstream integration has to be pursued. The existence of well-established vaccine manufacturers operating under a strong regulatory oversight will be critical to the viability of this strategy.

Recommended approach and tactics for each vaccine market

Following the assessment of the regional and global balance of supply and demand of each of the evaluated vaccines, specific preliminary recommendations have been developed for each of the vaccines in scope for further consideration during the pre-feasibility assessment planned for 2022.

Those recommendation include the most appropriate approach and the target production capacity.

Figure 33 – Current state of the PROSUR manufacturing landscape



These preliminary recommendations are to be considered with a portfolio view that considers the role of the different technology platforms, the existing manufacturing capacity, both of vaccine developers and CMOs, and the country readiness to be a recipient of a technology transfer. As such, each individual recommendation shall be taken as part of a broader concerted strategy that aims to support continued or improved access by PROSUR member states to COVID-19 vaccines, future pandemic preparedness and a sustainable strategy for regional supply self-sufficiency.

COVID-19 vaccine and future pandemic preparedness

CURRENT PLATFORMS: Inactivated, Subunit proteins, Nucleic Acid, Viral Vector

PROSUR TARGET CAPACITY (yearly universal booster): 300 million doses

Based on publicly available information, there is an estimated potential regional surplus in annual COVID-19 vaccine supply of ~300 million doses. This under the assumption that Viral Vector vaccines can be used as booster dose. The surplus in supply can be attributed to the number of CMOs in the region which are performing bulk production, formulation, filling and finishing manufacturing processes for COVID-19 vaccines developed outside the region. Nonetheless, no guarantee exists that CMO production will be made available to the region. Among the various platforms there are currently no manufacturers in the region performing bulk production for a COVID-19 vaccine using the mRNA platform technology. Recent efforts from PAHO to establish mRNA manufacturing Hubs in Brazil and Argentina are setting the foundation to address this shortcoming.

Due to the continued risk of pandemics or disruptive regional epidemics it is recommended that the capabilities for the full vaccine manufacturing cycle is established within the region for at least one flexible (“plug and play”) technology platform (e.g., nucleic acid or viral vector) in addition to one more traditional platform. A dual platform strategy will be valuable to (a) ensure broader pandemic response readiness that can be leveraged for other pathogens; (b) enable optionality in the COVID-19 vaccines that can be produced within the region to mitigate potential risks of reduced vaccine efficacy due to the emergence and spread of new SARS-CoV-2 variants. Furthermore, the inclusion of a traditional platform can leverage the capacities of existing manufacturers in the region.

It is recommendation that technology transfers are negotiated for bulk production of vaccines using the mRNA platform (already under development with PAHO) and subunit protein platforms. The subunit protein platform can be an area of focus for further vaccine development and manufacturing for the PROSUR initiative.

BCG vaccine

CURRENT PLATFORMS: Live-Attenuated

PROSUR TARGET CAPACITY (infant dose only): 14 million doses

Within PROSUR, there is demand for ~10 million doses of BCG vaccine per year and existing manufacturers are estimated to be capable of producing ~7 million doses of BCG vaccine per year, leaving a deficit of 3 million doses for regional self-sufficiently. BCG is a low-cost vaccine, and the manufacturing economics are challenging without high volumes, therefore establishing new manufacturers for BCG is not likely to be viable. Furthermore, the BCG vaccine technology is old and poorly characterised and need high biosecurity measures: all factors that make sharing processes extremely complicated.

It is recommended that PROSUR explore a potential increase in BCG production by one or several of the existing BCG manufacturers in the region based in Argentina, Brazil, and Colombia to cover the current sub-regional supply deficit. Alternatively, given the low cost of the vaccine, PROSUR could continue to address the gap between demand and local production capacity through

bilateral or regional procurement of BCG vaccine produced by vaccine manufacturers outside the region.

Pentavalent vaccine

CURRENT PLATFORMS: Toxoid, Inactivated, Subunit protein (all 3 since this is a combination vaccine)

PROSUR TARGET CAPACITY: 22 million doses

There is currently only one vaccine manufacturer in the LAC region capable of producing pentavalent vaccine, with an estimated ASC of ~4 million doses per year, these doses are reserved for the domestic market in Cuba. Demand for pentavalent vaccine within PROSUR is an estimated ~17.7 million doses per year, which is met through procurement from manufacturers outside the LAC region. Biomanguinhos, based in Brazil, has a pipeline candidate currently under development, which if successful could help to address some of the supply-demand imbalance within the sub-region, though production capacity is likely to be oriented to the domestic market in Brazil.

Pentavalent and Hexavalent vaccines are combination vaccines requiring multiple platforms, hence a larger effort to be able to produce in full the vaccine. It should be noted that vaccines containing Tetanus and Diphtheria antigens are also administered as boosters after the primary 3 doses series.

It is recommended that PROSUR negotiates with Instituto Butantan and Biomanguinhos to enhance production capacity for its pipeline pentavalent product to meet sub-regional demand, likely requiring a doubling of capacity from ~9 million doses to meet domestic pentavalent demand, to ~18 million doses to meet sub-regional demand.

If this increased production capacity is not possible, it is recommended that a technology transfer for bulk production, formulation, filling and finishing, from CIGB in Cuba or another pentavalent vaccine producer, is negotiated for a manufacture in the LAC region already capable of producing DTP vaccines, which could include ANLIS, based in Argentina, or BIRMEX, based in Mexico.

Pneumococcal conjugate vaccine

CURRENT PLATFORMS: Subunit protein (Conjugate)

PROSUR TARGET CAPACITY: 24 million doses

There is an annual supply deficit of ~4 million doses of PCV vaccine within PROSUR, under the assumption that PCV produced in the region is accessible to all countries. The manufacturing processes to produce PCV vaccines are complex, and only 5 vaccine manufacturers globally have licensed PCV products. Within PROSUR, 2 manufacturers have negotiated tech transfers to perform formulation, filling and finishing processes for PCV10 and PCV13 with commercialisation limited to their territory. Given the manufacturing complexities and limited number of other vaccines using similar production processes, it is not recommended that a new manufacturer in PROSUR establishes capabilities to manufacture PCV vaccines.

It is recommended that Biomanguinhos and Sinergium Biotech renegotiate existing technology transfer agreements to allow commercialization in all PROSUR countries and potentially to the entire LAC region. In a second step, an extension of the tech transfer should be pursued for bulk drug production for PCV vaccines and commercialize finished drug product within all PROSUR

countries. Such a technology transfer should be directed towards a new manufacturing entity located in the region, ideally in one of the most attractive geographies for tech transfers (e.g., Colombia or Chile). This would enable an extension of the manufacturing base in the region, and potentially, the setup of a distributed production model. Together, these strategies will enable the establishment of a strong sub-unit protein and conjugation vaccine platform within the region that can support production of several routine and pandemic vaccines.

Measles-containing vaccine

CURRENT PLATFORMS: Live-attenuated

PROSUR TARGET CAPACITY: 14 million doses

The supply-demand balance for MCV vaccines in PROSUR indicates a surplus of ~1 million doses, though this may be misleading as there is only one manufacturer in PROSUR producing MCV and available supply for commercialization is limited to the domestic Brazilian market. The global MCV market is dominated by few manufacturers based in India (for M and MR) and in the United States and Europe (for MMR and MMR-V). The global supply is balanced with demand requirements. However, MCV is produced using the live attenuated platform which is also used for many other routine vaccines which requires dedicated facilities for biosecurity reasons.

Due to the specificity of the manufacturing process, the use of combination MCV products in the region and the low scalability across the platform it is recommended that an extension of the commercialization rights for the existing manufacturer in the region is negotiated to address regional demand from the existing local supplier base.

Yellow fever vaccine

CURRENT PLATFORMS: Live-Attenuated

PROSUR TARGET CAPACITY: already available

There is an estimated annual supply-demand balance surplus of ~7 million doses of yellow fever vaccine among PROSUR countries. The 2 manufacturers in the region can produce ~26 million doses per year, meeting the demand requirements of PROSUR countries with excess supply being sold outside the region. Biomanguinhos has additional plans to expand production capacity of yellow fever vaccine to help stabilize global supply.

Due to the surplus in regional supply, there are no actions recommended to develop further manufacturing capabilities for yellow fever vaccines.

HPV vaccine

CURRENT PLATFORMS: Virus-Like Particle

PROSUR TARGET CAPACITY: 14 million doses

There is an annual supply deficit of ~2 million doses of HPV vaccine within PROSUR. Two manufacturers based in PROSUR countries have negotiated tech transfers to perform formulation, filling and finishing processes for HPV vaccines. Given the limited number of other vaccines using similar production processes (only Hepatitis B vaccine), it is not recommended that a new manufacturer in PROSUR establish capabilities to manufacture HPV vaccines.

It is recommended that PROSUR negotiates with Merck and Institute Butantan to have the latter producing adequate quantities of its pipeline HPV vaccine candidate to supply other countries in the region. This would enable all components of HPV production to take place within the region and for PROSUR countries to procure from a regional supplier.

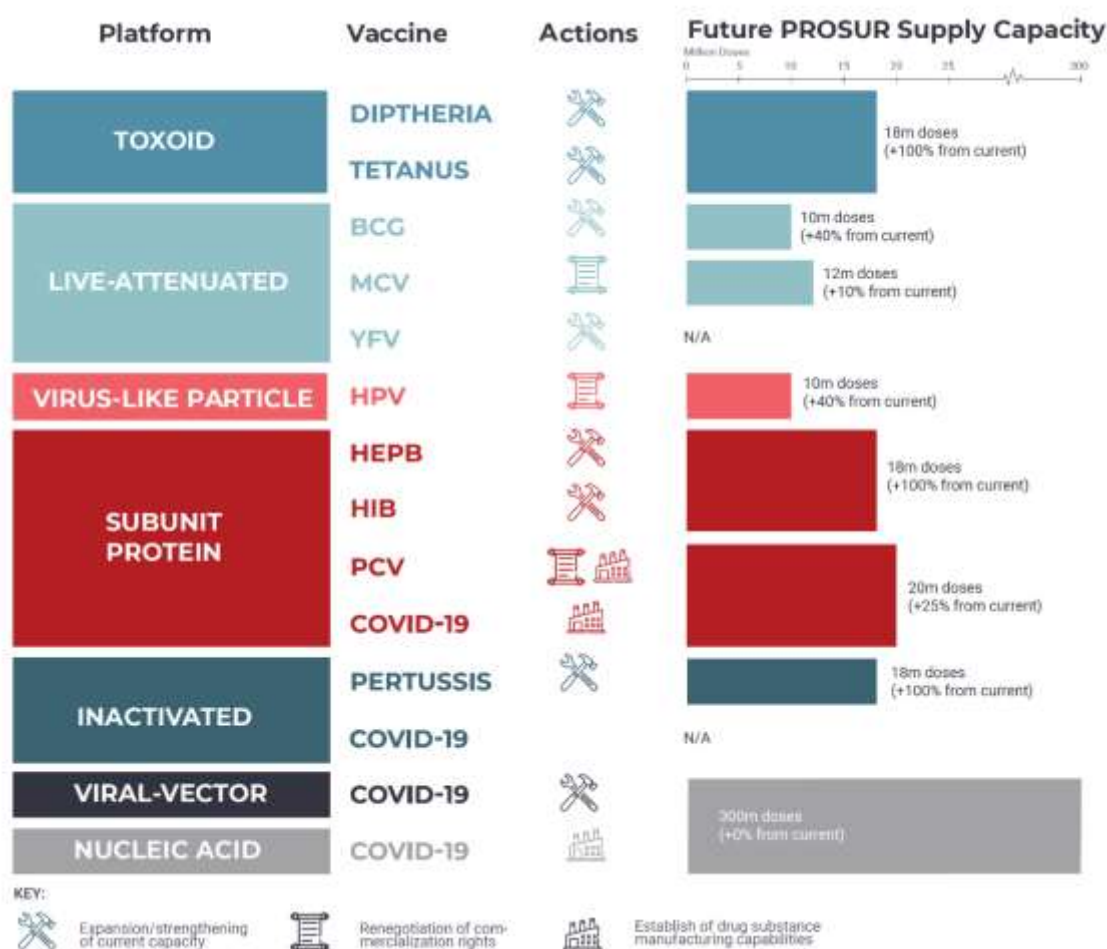
INFLUENZA vaccine

CURRENT PLATFORMS: Inactivated, Live-attenuated

The seasonal influenza vaccine market is in a very dynamic condition with different versions of the vaccine available – quadrivalent, trivalent – and others currently in development – improved versions delivering longer protection and universal ones. Currently, Influenza Vaccines are manufactured out of two different platforms: inactivated and live attenuated. Other platforms are used for vaccines currently in clinical development (e.g., nucleic acid, subunit proteins, viral vectors and VLPs). Influenza vaccination policies are also evolving with impact on target population and demand hence a full supply-demand balance is out of scope for a rapid diagnostic. Nonetheless, some basic recommendations can be formulated.

It is recommended that PROSUR perform an in-depth analysis of the future of the influenza vaccine market / policies with the goal of selecting a suitable platform (one between VLP, Subunit, Inactivated and Nucleic Acid) to produce seasonal and pandemic influenza vaccine consistently with the strategy defined for the EPI and COVID-19 vaccines.

Figure 34: Overview of recommendations for PROSUR



In summary, a regional strategy tailored to the market dynamics of each vaccine is recommended to address the existing regional vaccine supply imbalances. The strategy and recommended actions consider both the technical and market characteristics of each vaccine, the evolving trends in vaccine manufacturing and are based on the regional goal of self-sufficient vaccine manufacturing and access. There are three primary areas of strategic focus and action, with each area being relevant to a specific group of vaccines:

- The **establishment of bulk production manufacturing specific hubs** via the negotiation of technology transfers for the mRNA (already under development with PAHO) and subunit protein platforms. This can serve COVID-19 and PCV vaccine supply needs and lay the foundation for future other vaccines (such as Influenza)
- The **renegotiation of the commercialization rights** linked to technology transfers for the existing manufacturer in the region to be able to fully address regional demand from the existing local supplier base. This can serve MCV, HPV and PCV supply needs
- The **expansion/strengthening of the current existing capacity** to secure supply for existing routine and outbreak response vaccines. This pillar can serve BCG, YFV and Pentavalent vaccine

Additional regional vaccine ecosystem recommendations

The consolidated, vaccine-specific recommendations rely on a set of enabling factors within the broader vaccine ecosystem that are required for the success of the recommended actions and interventions. In the specific, five areas will require actions:

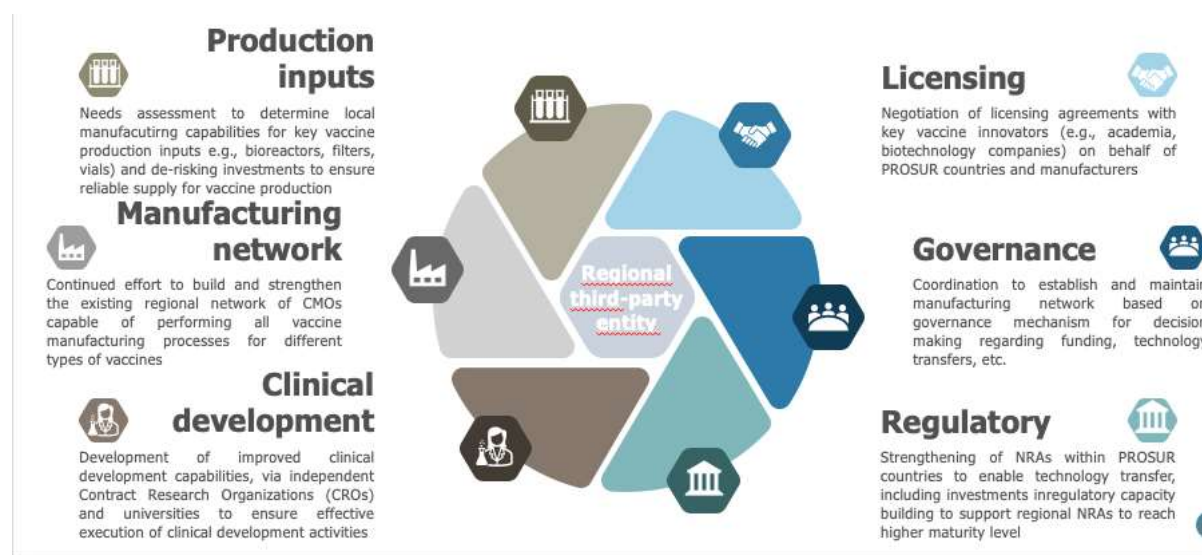
- **Licensing:** Despite technology transfers and licensing being directed towards a specific legal entity, these negotiations should be made with a regional focus. Therefore, it is recommended that a 3rd party entity is tasked with supporting the negotiation of licensing agreements with key vaccine innovators (e.g., academia, biotechnology companies) on behalf of PROSUR countries and manufacturers. This entity could also serve to support PROSUR countries to establish and contract services in a centralised and coordinated manner within and outside the region as required by specific vaccine manufacturing processes.
- **Regulatory:** The strengthening of NRAs within PROSUR countries is a precondition for any successful technology transfer. Investments, particularly in regulatory capacity building, will be required to ensure that NRAs in the region can attain the higher maturity levels required to provide stringent oversight on the manufacturing processes for vaccines.
- **Clinical development:** The development of more robust clinical development capabilities, in the form of independent Contract Research Organizations (CROs) and academic institutions within the region will be essential to ensure that effective execution of the required clinical development activities to achieve marketing authorisation, implementation monitoring, and design of new vaccine research and evaluation. By strengthening local capacity for clinical development, new vaccines can be designed and evaluated in ways that consider the specific requirements of the region.
- **Manufacturing:** A continued effort to build and strengthen the existing regional network of CMOs capable of performing all vaccine manufacturing processes for different types of vaccines can help to support regional vaccine manufacturing initiatives with local suppliers

who have developed or licensed key technologies and to assist with the production of vaccines for manufacturers outside the region.

- **Manufacturing input:** The success of strategic investments in vaccine technology and manufacturing capabilities is reliant on access to the key ingredients for the vaccine manufacturing process (e.g., bioreactors, filters, vials, etc.). Inability to access quality manufacturing inputs can jeopardise the production activities of even the most reliable vaccine manufacturers, as evidenced by recent challenges caused during the SARS-CoV-2 pandemic. There is currently very limited ability for local manufacturers to source these key inputs from suppliers local to the LAC region. A detailed assessment of the local manufacturers of inputs for the vaccine manufacturing process should be performed. Once gaps identified de-risking investments should be considered to facilitate the establishment of a reliable supplier base,. Build-up of regional capacity to produce key vaccine manufacturing inputs can provide other potential economic development opportunities to countries in the region which may not be suitable for investments in vaccine development and manufacturing.

Additionally, the input of an independent multi-country Technical Advisory or Steering Committee is recommended to provide technical guidance to the many decisions that will need to be taken across multiple domains. In that respect, PAHO's Regional Immunization Technical Advisory Group (RITAG) and other PAHO's regional technical advisory body can play an important role.

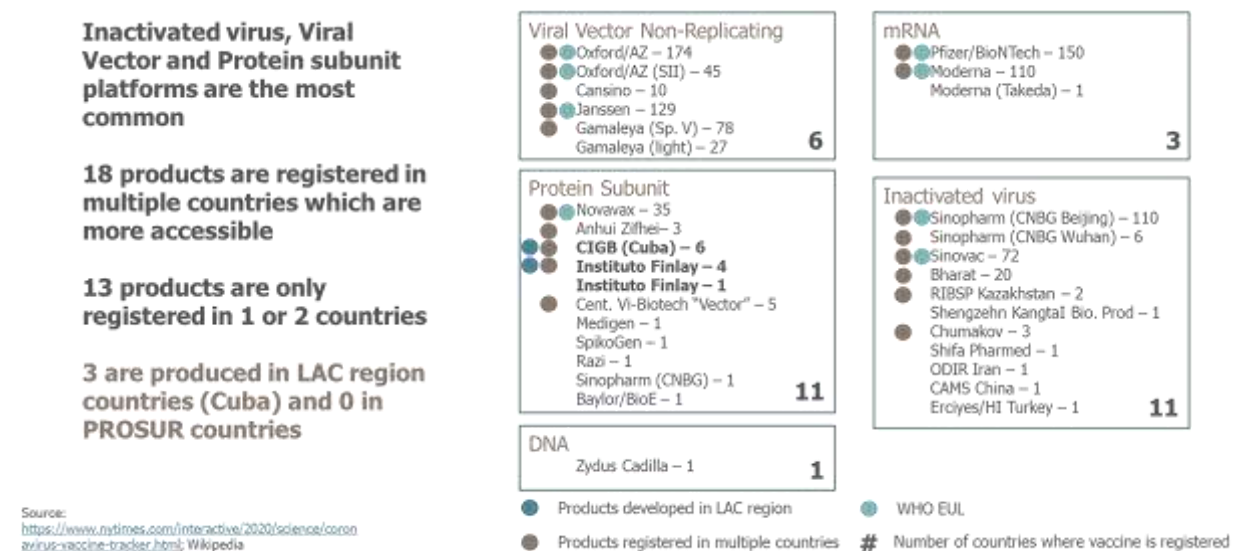
Figure 35: overview of the supportive framework



Together, those recommendations can support the development of an integrated strategy that brings together key stakeholders from a diverse range of sectors in multiple countries which form the basis of an interlinked and supportive ecosystem that provides PROSUR countries with the skills and capacities to improve the region's access to a reliable supply of lifesaving vaccines.

Annex 1

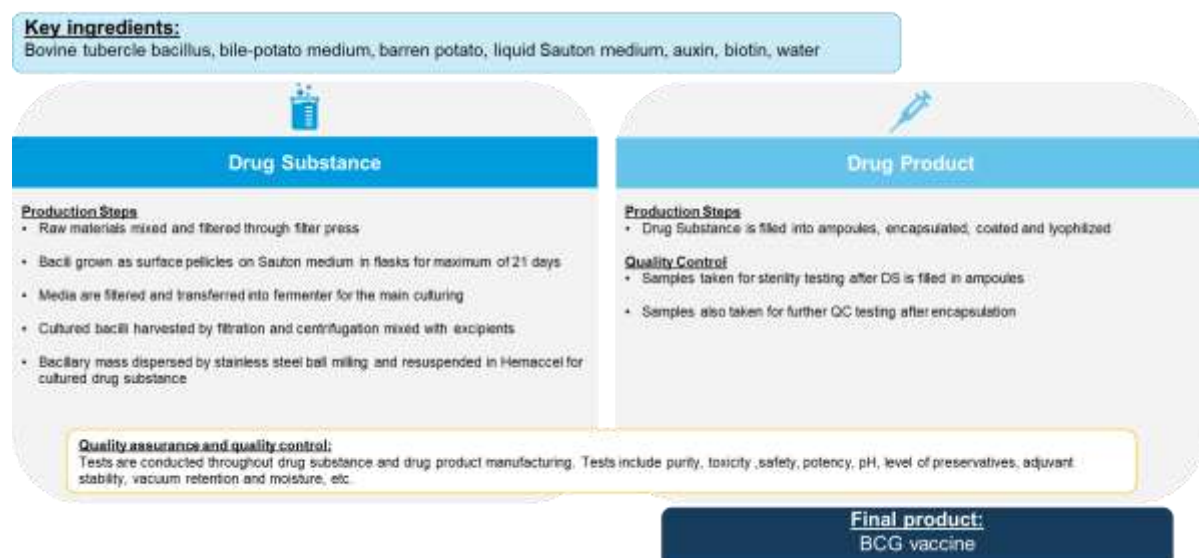
COVID-19 vaccines that have received regulatory approval, as of January 2022.



Annex 2

Vaccine manufacturing steps required to produce vaccines using in routine immunization by NIPs.

BCG



Pentavalent

Key ingredients:

Active ingredients (D,T,P, HepB surface antigen, conjugate of Hib capsular polysaccharide and tetanus toxoid), aluminum, aluminum hydroxide, aluminum phosphate, 2-phenoxyethanol, sodium chloride, Medium 199, Lactose, Pertactin, FHA

**Drug Substance****Production Steps**

- Diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins
- Acellular pertussis vaccine components obtained by extraction/purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of pertussis toxin by glutaraldehyde/formaldehyde treatment, and formaldehyde treatment of FHA and PRN
- The surface antigen of the HBV is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene coding for the major surface antigen of the HBV; the HBsAg is expressed in yeast cells and purified by several physico-chemical steps
- Fermentation of *Haemophilus influenzae* type b based on the seed lot principle; extraction and purification of PRP; activation of PRP with cyanogen bromide and adipic acid dihydrazide; coupling to purified tetanus toxoid; purification of the conjugate by size exclusion chromatography; dialysis

Quality assurance and quality control:

Tests are conducted throughout drug substance and drug product manufacturing. Tests include purity, toxicity, safety, potency, pH, level of preservatives, adjuvant stability, vacuum retention and moisture, etc.

**Drug Product****Production Steps**

- DTPa-HBV: Sterile adsorbed DT, PT, FHA, PRN and HBsAg concentrates mixed with a solution of sodium chloride and water for injections; sterile solution of 2-phenoxyethanol is added; adsorbed DTPa-HBV vaccine distributed aseptically in glass syringes.
- Hib: Active ingredient used for the preparation of the final bulk is the adsorbed PRP-T conjugate bulk. For preparation of final bulk sterile adsorbed PRP-T conjugate bulk is added to sterile concentrated lactose solution and resulting suspension is stirred and the pH is checked; final bulk is stored in sterile formulation tank between +2°C and +8°C and then filled in 3-ml capacity glass vials. Vials are then lyophilised, sealed with aluminium caps or Bioset caps and stored at +2 to +8°C.

Final product:
Pentavalent vaccine

PCV**Key ingredients:**

Polysaccharide for each pneumococcal serotype, CRM197 protein, aluminum phosphate adjuvant, sodium chloride, succinic acid, polysorbate 80

**Drug Substance****Production Steps**

- Working seed is thawed and expanded in Soy media with Dextrose/Magnesium Sulfate; culture is terminated by lysing the cells with the addition of Sodium Deoxycholate solution
 - Similar, separate process employed for polysaccharides of all 13 serotypes
- Polysaccharides are then purified using precipitation, dialysis and chromatography steps → Purified polysaccharides are filtered and stored in stainless steel drum at -20°C
- Activation of polysaccharides by partial oxidation of adjacent hydroxyl groups in carbohydrate repeat units using sodium periodate
- Conjugation: reaction performed in non-aqueous DMSO and in aqueous medium which is initiated by addition of sodium cyanoborohydride solution; bulk conjugate diluted to target concentration before dispensing into flexible containers

Quality assurance and quality control:

Tests are conducted throughout drug substance and drug product manufacturing. Tests include purity, toxicity, safety, potency, pH, level of preservatives, adjuvant stability, vacuum retention and moisture, etc.

**Drug Product****Production Steps**

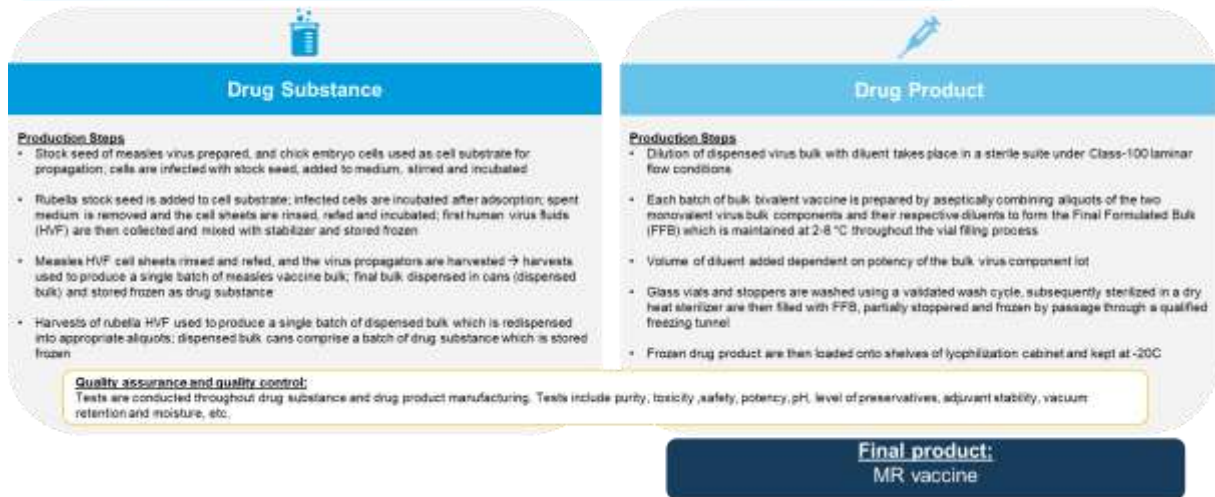
- 13 conjugates are added to mixture of Succinate/Sodium chloride buffer and polysorbate 80 and sterile filtered
- Solution is then mixed with Aluminium phosphate suspension and stirred
- Adsorbed vaccine is then filled in pre-filled syringes

Final product:
PCV 13-serotype

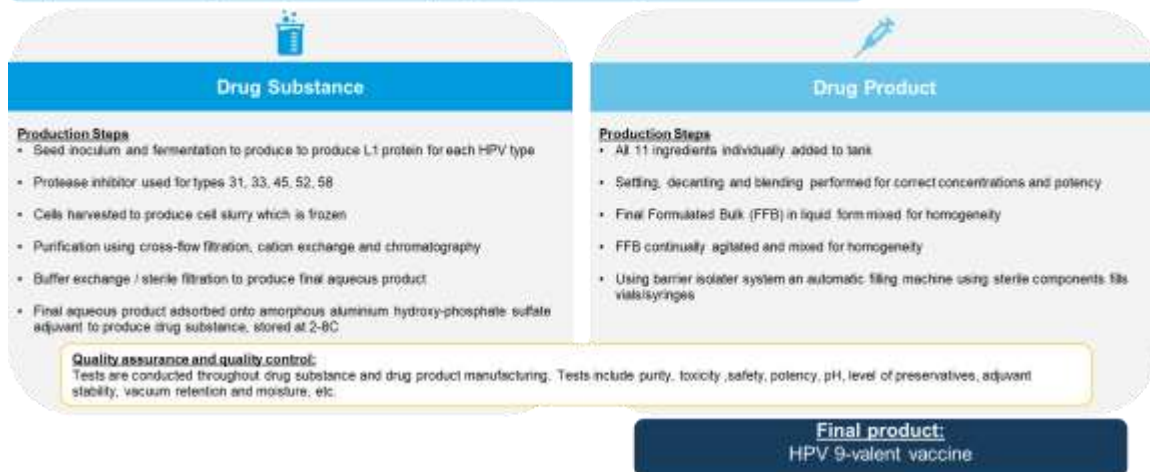
Measles-Rubella

Key ingredients:

Measles virus, rubella virus, sodium and potassium phosphate (mono/dibasic), sodium bicarbonate, medium 199, minimum essential medium (Eagle), neomycin, phenol red, sorbitol, gelatin, sucrose, monosodium L-glutamate

**HPV****Key ingredients:**

L1 protein for each HPV type, amorphous aluminium hydroxyphosphate sulfate adjuvant, sodium chloride

**Vaccine platform technology manufacturing timelines**

