RNA-Based Vaccine Manufacturing: Infrastructure, Regulations, and Global Implications

Fabricação de vacinas de RNA: Infra-estrutura, regulamentos e implicações globais

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ABSTRACT

RNA-based vaccines have emerged as a powerful tool in the fight against infectious diseases, including the recent COVID-19 pandemic. However, their successful production requires properly designed facilities for RNA synthesis, purification, and formulation. This review article explores the facility requirements, regulatory aspects, and global implications of specialized RNA vaccine production. It highlights the importance of Good Manufacturing Practice (GMP), equipment and technology in the production process, providing a critical analysis of collaborations, investments, and the establishment of RNA plants around the world. Finally, it addresses the challenges faced by low- and middle-income countries and the role of the "tripod" production model involving collaboration between university, industry, and government. Overall, this document clarifies the most relevant aspects of RNA-based vaccine manufacturing, emphasizing the need for quality, safety, and scalability to meet global health demands.

Keywords: RNA Vaccines; Vaccine Manufacturing Infrastructure; Regulatory Compliance; Equitable Vaccine Distribution.

RESUMO

As vacinas baseadas em RNA surgiram como uma ferramenta poderosa na luta contra as doenças infecciosas, incluindo a recente pandemia de COVID-19. No entanto, a sua produção bem-sucedida requer instalações devidamente concebidas para a síntese, purificação e formulação de RNA. Este artigo de revisão explora os requisitos das instalações, os aspectos regulamentares e as implicações globais da produção especializada de vacinas de RNA. Destaca a importância das Boas Práticas de Fabricação (BPF), do equipamento e da tecnologia no processo de produção, fornecendo uma análise crítica das colaborações, dos investimentos e do estabelecimento de fábricas de RNA em todo o mundo. Por fim, aborda os desafios enfrentados pelos países de baixo e médio rendimento e o papel do modelo de produção "tripé" que envolve a colaboração entre a universidade, indústria e governo. De um modo geral, este documento esclarece os aspectos mais relevantes do fabrico de vacinas com base em RNA, salientando a necessidade de qualidade, segurança e escalabilidade para satisfazer as exigências da saúde mundial.

Palavras-chave: Vacinas de RNA; Infraestrutura de fabrico de vacinas; Conformidade regulamentar; Distribuição equitativa de vacinas.
INTRODUCTION

RNA-based vaccines have emerged as a groundbreaking immunization approach, revolutionizing how we combat infectious diseases (MACHADO et al., 2021). In contrast to traditional vaccines, which rely on weakened or inactivated pathogens, RNA-based vaccines leverage genetic material to provoke an immune response. These vaccines employ messenger RNA (mRNA) molecules to carry the genetic instructions for cellular production of specific target proteins, thereby prompting the immune system to recognize and mount a defensive response against the targeted pathogen (RAUCH et al., 2017).

The COVID-19 pandemic served as a pivotal moment, underscoring the significance of RNA-based vaccines. Given the global consensus that mass vaccination was the most effective strategy to control the spread of SARS-CoV-2, an unprecedented multinational effort was observed, resulting in the rapid development of vaccine candidates and the initiation of clinical trials (KOIRALA et al., 2020; MACHADO et al., 2022). The mastery of the RNA platform allowed a revolution in the vaccine pharmaceutical industry, where its production was carried out in record time: only one year after the identification of the new coronavirus, the first vaccine had already obtained authorization from the United States (U.S.). Food and Drug Administration (FDA) for emergency use. This can be largely attributed to the favorable safety profiles of RNA-based vaccines, their production efficiency, and the extensive body of prior research (BRISSE et al., 2020).

It is important to highlight that the main innovations in vaccine technology that use RNA are related to the construction of new RNA sequences. For this reason, RNA technology is also being used to develop treatments for influenza, different types of cancer, infectious and neglected diseases, as well as in vaccines (AWASTHI et al., 2019; MCKAY et al., 2020). However, the large-scale production of RNA-based vaccines poses challenges due to the need for specialized facilities, advanced technical capabilities, and constraints in the supply of essential raw (BLAKNEY; IP; GEALL, 2021; VAN DE BERG et al., [s. d.]). Therefore, highlighting the importance of developing technology platforms that can produce not only RNA but also carriers and adjuvants for vaccines and medicines stands out materials especially in low-and middle-income countries.

Considering this, this article sheds light on the intricate landscape of RNA-based vaccine manufacturing, navigating the challenges posed by specialized production, regulatory landscapes, and global inequalities. By addressing the challenges associated with large-scale production and equitable distribution of RNA-based vaccines, it further
explores the pressing need for technology platforms that support the entire vaccine production process.

**RNA-Based Vaccine Development**

Traditional methods for vaccine production have notable advantages. For instance, the production based on inactivated viruses or bacteria often comes with a well-established safety record that contributes to a high level of confidence of such vaccines. Additionally, protein-subunit vaccines, while facing challenges in inducing a robust immune response, have been successfully employed in various vaccines and are known for their targeted and specific approach to immunization. However, these methods require high investment costs in addition to having reduced scaled capacity and do not offer potential solutions to respond quickly to pandemic situations since it depends on egg production capacity.

On the other hand, the technological basis of RNA-based vaccines is characterized by their easy process manufacturing, safety, and immunization efficacy. The platform is versatile and adaptable to multiple targets, and it is easily adjusted to other diseases by simple modification of the RNA molecules (ULMER; MANSOURA; GEALL, 2015). These vaccines do not have animal products or viral genomes in their composition since they are produced with synthetic materials by molecular biology techniques, reducing allergic reactions and interactions with the host cell genome (MARUGGI et al., 2019a).

It is important to highlight that the discovery and utilization of the RNA platform for therapy were made possible through the pioneering work of Kariko and Weissman (KARIKÓ; BUCKSTEIN; NI, 2005; TO; CHO, 2021). Their research identified mRNA's capacity to activate the immune system via Toll-like receptors (TLRs), and they demonstrated that minor structural modifications could render RNA safe for human therapeutics, facilitating the production of substantial proteins. Subsequently, numerous studies have been conducted to optimize RNA (HOLTKAMP et al., 2006; HOMMA; NOGUCHI; FUKUCHI, 2016; KIM, Sun Chang et al., 2022). This level of advancement has enabled RNA technology to be employed not only in the development of new vaccines but also in a wide range of therapies, particularly in anti-tumor treatments.

In the context of RNA vaccines, there are, to date, two types of technology used so far: conventional (messenger RNA, mRNA) and self-amplifying (saRNA). The conventional RNA strategy refers to non-amplifying mRNA and has been widely used against cancer (PARDI et al., 2018). On the other hand, vaccines that use saRNA, present
RNA sequences that code for specific non-structural virus proteins and confer a self-replicating property to the molecule (COMES; PIJLMAN; HICK, 2023). This platform, also known as new-generation vaccines, is effective in potentiating humoral and cellular immune responses against antigens in different pre-clinical models (BALLESTEROS-BRIONES et al., 2020).

In addition to innovations in technology associated with the construction of new RNA sequences, the development of materials that provide these sequences efficiently and safely have made it possible to expand this immunization modality (KIM, Byungji et al., 2023; SCHLAKE et al., 2012). Given the susceptibility of RNA molecules to degradation due to factors such as ribonucleases (RNAses), lipid nanoparticles (LNPs) emerge as a critically important strategy to ensure the effective functionality of RNA vaccines (KON; ELIA; PEER, 2021; TENCHOV et al., 2021). Considered an essential tool in the pharmaceutical industry since the 1970s, LNPs possess the ability to encapsulate drugs and deliver therapeutics with precision to specific locations in the body. This versatility has rendered them valuable for treating a wide range of diseases (HALD ALBERTSEN et al., 2022; WANG; ZHANG; DONG, 2021). In RNA vaccine technology, they are designed to protect RNA payloads from degradation and facilitate their efficient delivery to target cells (HALD ALBERTSEN et al., 2022). Both the Pfizer-BioNTech and Moderna mRNA vaccines incorporate LNP formulations in their composition, with the main difference being the proportions of lipids used. Additionally, RNA vaccines currently in the developmental stages also employ lipid nanoparticle carrier technology, further emphasizing the importance of this technology in the realm of RNA vaccines (CHEN et al., 2022; HALD ALBERTSEN et al., 2022; POLACK et al., 2020).

Due to these substantial investments made by pharmaceutical companies in research and development, advancements in technology have led to the successful studies and development of RNA-based vaccines. Notable examples include the Pfizer-BioNTech and Moderna vaccines, both developed in response to the COVID-19 pandemic (ZHANG et al., [s. d.]). These vaccines share similar mRNA chemical modifications and coding for the spike protein. Moreover, RNA technology has been extensively applied in the development of vaccines for diseases lacking effective therapies, such as malaria, tuberculosis (LUNDSTROM, [s. d.]) HIV (KHALID et al., 2021), and rotavirus (FIX et al., 2020a). The rapid development and distribution of vaccines are crucial to mitigate these and other diseases. Therefore, the establishment of plants that
incorporate the technology used for the rapid, cost-effective development and manufacturing of low-cost, large-scale vaccines is critical to meet global demands for emerging disease pandemics, as well as other diseases of public health concern.

RNA Vaccines Manufacturing Infrastructure

RNA manufacturing process and production facilities

RNA vaccines represent an innovation in the process of producing medicinal substances. As an innovative form of treatment, achieving large-scale production of mRNA poses significant challenges and demands advanced manufacturing technologies. The production of mRNA on a large scale involves intricate manufacturing stages, and currently, various methods are employed, including chemical, recombinant, or enzyme-based systems (WEBB et al., 2022). Among the factors necessary for the manufacture of RNA vaccines, it is important to consider the level of biosafety required, current GMP requirements, and the layout of the facility which must be very well planned to optimize workflow and eliminate the risk of contamination (WORLD HEALTH ORGANIZATION, 2021). To do these facilities dedicated to vaccine production require clean room areas where the concentration of transported particles, humidity, temperature, and pressure are extremely controlled (LARSEN; BALDWIN; COLER, 2023). ISO class 7 is generally used for RNA vaccine production; however, it is worth noting that each manufacturing operation requires a specific classification (WORLD HEALTH ORGANIZATION, 2011).

In addition, it is important to ensure on layout that the different stages of operation are separated. The isolation of the RNA synthesis, purification, formulation, and packaging areas helps to minimize the risk of contamination, significantly increasing the safety profile and integrity of the final product (VICKERS et al., 2022). As shown in Figure 1, there are three main phases in the production of RNA vaccines which must be carried out in environments that are isolated from each other: 1) production of the pharmaceutical substance (also known as bulk production, primary manufacturing, or upstream), 2) purification of the active substance (downstream), and 3) manufacturing of the pharmaceutical product (also known as fill-finish) (KIS, Zoltán; KONTORAVDI; SHATTOCK; et al., 2020; KIS, Zoltan; RIZVI, 2021).
Figure 1. Workflow Diagram for RNA Vaccine Production. The step-by-step process involved in producing RNA vaccines. The workflow begins with RNA synthesis by in vitro transcription (IVT) in the upstream phase, followed by the purification of the pharmaceutical substance. The downstream or second manufacturing stage involves the formulation of the RNA into lipid nanoparticles. Finally, the product manufacturing, also known as fill-finish, takes place. TFF: Tangential Flow Filtration; Chrnt: Chromatographic purification.

Adapted from (KIS, Zoltán; KONTORAVDI; DEY; et al., 2020).

Upstream processing refers to the stage at which RNA is produced and synthesized through evidence of IVT, recognized as the gold standard for large-scale mRNA synthesis. (KIS, Zoltán; KONTORAVDI; SHATTOCK; et al., 2020). This method utilizes RNA polymerases derived from bacteriophages, along with chemically modified ribonucleoside triphosphates (rNTPs), for efficient mRNA synthesis. However, it has two significant limitations: the requirement for a sequence-specific promoter, limiting 5′ modifications, and terminal heterogeneity caused by nonspecific runoff by RNA polymerase (WEBB et al., 2022). This occurrence begins with the inclusion of all necessary components for the occurrence in the bioreactor (KIS, Zoltán; KONTORAVDI; SHATTOCK; et al., 2020). After RNA synthesis, the enzyme DNAse I is added to the bioreactor to digest the template DNA and the reaction mixture leaves the bioreactor and enters the downstream processing section (KIS, Zoltán; KONTORAVDI; DEY; et al., 2020). IVT’s main advantage lies in its independence from the template DNA sequence, allowing a versatile production process for various mRNA types. This characteristic potentially accelerates regulatory approvals for new therapeutic substances (WEBB et al., 2022). Although the cost of acquiring the necessary materials is high, due to the limited number of primary suppliers with the required certification, it is estimated that the speed and practicality of this production process reduces the added value of production compared to cell-based products (SOUZA ROSA et al., [s. d.]). Nevertheless, IVT currently stands as the cutting-edge technology for large-scale, cell-free mRNA production.

Next, downstream processing occurs, which is necessary to remove impurities, simultaneously reduce bulk volume, and concentrate the desired product from the bioreactor. This step is critical to ensure biologically active and therapeutically viable
mRNA. While laboratory-scale mRNA purification involves the use of DNases to eliminate DNA, followed by lithium chloride precipitation for isolation, large-scale production of clinical-grade mRNA requires a more sophisticated downstream processing (DSP) approach (WEBB et al., 2022).

During downstream processing, several steps are implemented to recover the final product. Throughout the purification (downstream) process, tangential flow filtration (FFT) can trap the RNA molecule letting smaller components flow through the filter. The retained RNA is then purified by a sequence of chromatography that removes protein enzymes (KIS, Zoltán; KONTORAVDI; DEY; et al., 2020). A second step of FFT is performed so that the buffer is replaced by the formulation buffer characterizing the entry into the lipid nanoparticle (LNP) encapsulation operation unit (HOU et al., 2021). Finally, the encapsulated RNA goes through a third FFT cycle for diafiltration and subsequent filtration under sterile conditions. The sterile LNP-encapsulated RNA solution is then transferred to the fill-finish section (KIS, Zoltán; KONTORAVDI; DEY; et al., 2020). The final formulated RNA is then filled into closed and sealed vials or other containers that will be labeled and packaged for further inspection by quality control (HOU et al., 2021).

It is important to note that conventional vaccine technologies that are cell-based require cell growth in large bioreactors (e.g., 2000 L), whereas RNA-based vaccines can occur in much smaller bioreactors (e.g., 30 L to 50 L) (SOUZA ROSA et al., [s. d.]). Recently, it was estimated by bioprocess modeling software the amount of equipment and plant/operating area required to produce 100 million doses per year of 2 RNA vaccines (HARRISON et al., 2015). The results revealed the requirement for a bioreactor with a working capacity of approximately 5 L for this production for both vaccines (30 µg per dose vaccine) (KIS, Zoltán;; RIZVI, 2021; SOUSA ROSA et al., [s. d.]).

All production processes take place in different locations and require different equipment, facilities, quality control methodologies, and expertise (KIS, Zoltán; KONTORAVDI; DEY; et al., 2020). However, because they differ only in the RNA sequence, vaccines against practically any disease can be produced using the same production process (KIS, Zoltán; KONTORAVDI; SHATTOCK; et al., 2020).

Evaluating the current vaccine production structure available, the capacity to accommodate the production of RNA technology is greater when compared to the processes required in the production of cell-based vaccines (PARDI et al., 2018). Because they are considered small-scale production, RNA-based vaccines require a smaller
facility in terms of area, initial capital investment, and construction time [52]. The space dedicated to the equipment and utilities needed to produce RNA vaccines corresponds to only 25% of the manufacturing plant, while the other 75% is dedicated to supporting areas (DENAUDT; COQUET; DODELET, 2008). In this sense, it is expected that only the production areas will be generated in facilities already operating in the production of other vaccines, monoclonal antibodies, insulin, veterinary vaccines, and other biological and injectable products (ROSA et al., 2021), with the existing support areas being shared by the receiving facilities.

**Regulatory frameworks**

Like in all types of vaccines, RNA vaccine development and testing include preclinical, clinical, and registration steps (VACCINE DEVELOPMENT, TESTING, AND REGULATION | HISTORY OF VACCINES, [s. d.]). The preclinical stage involves basic laboratory research and animal experiments to identify potential vaccine candidates and evaluate their safety, immunogenicity, and potential efficacy. The data gathered from these tests help researchers determine whether the vaccines are suitable for human trials. Then, the vaccines follow a phased approach to clinical trials to confirm efficacy, safety, and monitor any rare adverse events (RAWAT; KUMARI; SAHA, 2021). Evaluation of all processes and data received is carried out by regulatory agencies proving the quality, efficacy, and batch safety and helping for their release and commercialization after GMP certification (PENG et al., 2020).

It is important to note that even after regulatory approval or authorization, ongoing monitoring and pharmacovigilance activities continue. This includes monitoring vaccine safety, efficacy, and long-term effectiveness, as well as assessing any changes in the manufacturing process or product formulation instilling confidence in their use and providing assurance to the public (KNEZEVIC et al., 2021). These regulatory aspects ensure that RNA vaccines meet stringent standards for safety, efficacy, and quality, instilling confidence in their use and providing assurance to the public. Collaboration between vaccine developers and regulatory agencies is crucial throughout the development and manufacturing process to ensure compliance with regulatory requirements (NAIK; PEDEN, 2022).

The growing need for safe vaccines requires deeper oversight that involves establishing and enforcing international guidelines (KNIPE et al., 2020). In emergencies, such as the COVID-19 pandemic, many of these guidelines were softened and the
manufacturing plant establishment was happening simultaneously with other steps in the manufacturing process. In some places, technology transfer (such as procurement of equipment, materials, and validation testing) was happening in parallel with submission to regulatory agencies (JOE et al., 2022). This scenario was observed in Brazil, for example, where the emergency public health situation enabled a race in domestic vaccine production for technology transfer, while import negotiations for vaccines and supplies were taking place (FONSECA; SHADLEN; ACHCAR, 2023).

**RNA factories worldwide and necessary investment**

The investment in RNA technology development has been experiencing substantial growth (TOMBÁCZ; WEISSMAN; PARDI, 2021). This surge in financial support is directed towards enhancing therapeutic modalities, particularly in the realm of vaccines. Most RNA facilities in the world are based particularly in developed countries and have governmental, private (when technology transfer occurs), and/or non-governmental non-profit foundation investments (HAYMAN; KUMAR SURI; DOWNHAM, 2022; ROSA et al., 2021). For example, the U.S. invests over $50 billion annually towards R&D (DE RASSENFOSSE; JAFFE; RAITERI, 2019), through its Operation Warp Speed initiative, allocated significant funding to support the establishment of RNA vaccine production facilities (OPERATION WARP SPEED: IMPLICATIONS FOR GLOBAL VACCINE SECURITY LANCET COMMISSION ON COVID-19 VACCINES AND THERAPEUTICS TASK FORCE MEMBERS*, [s. d.]). This investment aimed to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, including RNA-based vaccines (KIM, Jerome H.; MARKS; CLEMENS, 2021; NEUMANN et al., 2021). The COVID-19 pandemic has further emphasized the importance of government funding in vaccine development. Countries such as Canada (185 million dollars), the United Kingdom (315 million dollars), Germany (322 million dollars), China and India have invested not only in vaccine development but also in modernizing manufacturing facilities to guarantee the supply of vaccines and reduce the need for imports (CUREVAC, 2022; DE NEGRI; DE HOLANDA; SQUEFF, 2014).

On the other hand, it's worth noting that public investment in R&D has been extremely low in low- and middle-income countries. In Brazil, for example, only $4000 was earmarked for this purpose until mid-2020 (OLIVEIRA, 2021). This disparity in investment highlights the challenges faced by these countries in building and strengthening their research capabilities, particularly in emerging fields such as RNA
vaccine development. For this reason, it is crucial for governments, especially in low and middle-income countries, to recognize the importance of increased investment in R&D to foster scientific advancement, innovation, and self-sufficiency in vaccine production. By allocating adequate resources and funding, governments can support the development of domestic research capabilities, enhance scientific infrastructure, and contribute to global health security.

Regarding investments by private foundations, the Bill & Melinda Gates Foundation (BMGF) stands out as a notable example (SAVAGE, 2021). By the year 2015, the foundation had already invested a total of $52 million in CureVac, in addition to supporting other companies such as BioNTech, Scripps, and Moderna in developing vaccines against malaria, tuberculosis (NCT04556981), HIV (NCT04725877), and rotavirus (FIX et al., 2020b). In a further step, the funding ensures the progress of various RNA research and points to the platform as a promising strategy for the development of vaccines and treatments for diseases that do not yet have effective therapy.

An initiative created in 2020 by the Coalition for Epidemic Preparedness Innovations (CEPI) features a global collaboration between public, private, and philanthropic institutions that have the goal of developing vaccines to contain epidemics and pandemics (DE NEGRI; KOELLER, 2020). During the COVID-19 pandemic, the institution, which is supported by several countries such as Australia, Belgium, Denmark, Ethiopia, and Germany, focused all its efforts on shortening the development, production, and exposure to immunizations, as well as diagnostic tests and new therapies.

Although it is difficult to obtain details about the revenues and market value of the RNA vaccines manufacturers, due to their insufficient transparency and degree of confidentiality of each facility, analyses of financial reports from some companies reveal how much was invested in RNA vaccines during the pandemic (WOUTERS et al., 2021)

Analyzing the companies involved in RNA vaccine manufacturing, we can draw several key conclusions. Firstly, the production of RNA-based vaccines is a global endeavor, with companies and facilities located in various countries worldwide. This highlights the widespread recognition of the significance of RNA vaccines in addressing infectious diseases on a global scale (FONSECA; SHADLEN; ACHCAR, 2023). Furthermore, the involvement of different types of organizations in RNA vaccine manufacturing is notable. These companies include pharmaceutical companies, contract development and manufacturing organizations (CDMOs), and biotechnology firms, highlighting the collaborative nature of the industry. The significant investments made in
establishing dedicated facilities for RNA vaccine production demonstrates a long-term commitment to this technology (JACKSON et al., 2020).

In promoting a comprehensive approach to global health, it is essential to draw attention to the absence of RNA vaccine manufacturers from the South American and African continents. This observation emphasizes the importance of fostering technology transfer and increasing investments in the pharmaceutical and biotechnological industries in these regions. By encouraging collaboration, regulatory frameworks, and infrastructure support, we can collectively work towards ensuring a more equitable distribution of expertise and resources, ultimately contributing to the global effort in addressing health challenges through RNA vaccine manufacturing. Along with government and/or non-governmental non-profit foundation support, through financial investments, regulatory frameworks, and infrastructure support, these efforts play a crucial role in enabling RNA vaccine manufacturing. Collectively, they contribute to the advancement of RNA vaccine manufacturing capabilities, allowing to production of safe and effective vaccines to address global health challenges.

The COVID-19 pandemic has highlighted the need for the presence of RNA vaccine factories in low and middle-income countries, as they increase the availability of vaccines, reducing import dependency and strengthening domestic production capacity (Figure 2).

**Figure 2.** Importance of RNA vaccine plants in developing countries and key impacts and benefits that arise from the installation of such factories in low- and middle-income countries.
Most vaccines are produced in developed countries, resulting in unfair and unequal distribution. In 2009, when the first influenza pandemic was reported, 80% of the vaccines produced were distributed among the already industrialized countries: the U. S., Canada, Australia, Europe, China, Russia, and Japan (POLICY CURES RESEARCH, 2021). Only after nine months of the pandemic state declaration by the World Health Organization (WHO), did vaccines begin to be distributed to low and middle-income countries. Interestingly, these countries suffered the most due to poor health system conditions and the difficulty in implementing infection prevention strategies, such as social isolation measures and the required informal work for survival (THE LANCET, 2021). A similar scenario was observed during the current pandemic of COVID-19 where most vaccines were initially targeted at high-income countries a phenomenon known as vaccine nationalism (JOE et al., 2022). As of August 9, 2021, 0.3% of the 4.46 billion doses had been administered in low and middle-income countries, contrasting with the 82% of doses administered in developed countries (THE LANCET, 2021).

In addition to the centralization of production, supply shortages followed by the greater purchasing power of wealthy countries made universal access to vaccines difficult during peak disease transmission. Given the concentration in the supply of vaccines in the U.S. and Europe, leaders of the territories of Latin America, Africa, the Middle East, and Asia have turned to vaccines developed by Chinese and Russian manufacturers (CYRANOSKI, 2020; LEDFORD; CYRANOSKI; VAN NOORDEN, 2020). The need, highlighted during the current pandemic, to increase vaccine production to meet global demand is a major challenge.

The establishment of RNA plants in low and middle-income countries offers opportunities to transfer technology and expertise. This includes training local personnel, sharing advanced manufacturing practices, and establishing partnerships with international companies and research institutions. During the pandemic of COVID-19 the development and research sectors of all countries were challenged as, due to its magnitude, imports of health products and supplies were limited by international market shortages (ROSA et al., 2021). Interestingly, countries with better-established production systems were those that most avoided raw material shortages and consequently better responded to fighting the pandemic (ROSA et al., 2021). In this context, technology transfer presents itself as a solution to the production bottleneck allowing for expansion in manufacturing capacity (FONSECA; SHADLEN; ACHCAR, 2023). In addition,
knowledge sharing also promotes the rapid execution of consolidated and standardized practices in the industrial sector.

More recently, an mRNA technology transfer center was created to help low- and middle-income countries produce their vaccines and expand their capacity to manufacture other products such as drugs and diagnostics to provide health coverage in line with their health priorities (CHOONARA et al., 2023). In Africa, the technology delivery platform relied on the technology center at Afrigen Biologics’ facility in Cape Town, South Africa, in partnership with the South African Medical Research Council (South African Medical Research Council - SAMRC) and local vaccine producer Biovac (CHOONARA et al., 2023). Additionally, the partners provided all financial and training assistance for the development of the vaccines at all stages. The project is estimated to be expanded to five more African countries: Egypt, Kenya, Nigeria, Senegal, and Tunisia. BioNTech and Moderna have also set up their plants on African territory (COHEN, 2022). The WHO initiative to create a hub for RNA vaccines emerges as another attempt to increase vaccine production on the hitherto less vaccinated continent for COVID-19 while also opening prospects for application in other endemic infectious illnesses like tuberculosis and HIV.

Other manufacturers' sharing of knowledge and technology with middle-income countries, including the partnerships established between AstraZeneca and Brazil (Fiocruz), India, Argentina (mAbxience), and Thailand (Siam Bioscience); Johnson & Johnson with South Africa (Aspen Pharmacare); Novavax with India; and Arcturus Therapeutics with Vietnam (Vinbiocare) enabled the rapid production of vaccines against coronavirus (RIECKERMANN, 2022).

It is worth noting that the creation of manufacturing plants enabled the consolidation of technology transfer and knowledge internalization and enhanced domestic production of the immunobiological of interest (FONSECA; SHADLEN; AHCAR, 2023). Through the incorporation of 022 technology for local production, quality control analysis (of the API and the lipidic carrier), as well as the inclusion of analytical techniques and stability studies employed, the production efficiency is impacted in such a way that both the updating of current vaccines (that lose their efficiency due to viral mutations) and the design of bi- or multivalent vaccines that aim to protect against multiple variants is improved (KAVANAGH; GOSTIN; SUNDER, 2021).

Ecosystem for Development and Production
In the context of asymmetrical globalization and analysis of barriers that maintain inequalities and vulnerability in middle- and low-income countries development and production ecosystems, it is crucial to consider the Health Industrial Economic Complex (HIEC) model (GADELHA, Carlos Augusto Grabois; TEMPORÃO, 2018). HIEC is an institutional, political, economic, and social ecosystem within which health production and innovation occur (GADELHA, Carlos Augusto Grabois; TEMPORÃO, 2018). The interdependence between health-related activity production and innovation dynamics defines this ecosystem as the interface between national health systems and national innovation systems.

The HIEC production and innovation space is the central ecosystem in which the conflict between capital interests and social objectives is manifested in health (GADELHA, Carlos A. Grabois, 2021; GADELHA, Carlos Augusto Grabois; TEMPORÃO, 2018). In summary, the morphology of the HIEC is composed of industry and a services subsystem that connect and are promoted and regulated by the local government. While the industrial sectors comprise the chemical and biotechnology facilities, in addition to the basic industry (mechanical, electronics, and materials), the delivery services encompass all public medical services and health care (hospitals, outpatient clinics, diagnostic services, retail, and distribution (GADELHA, Carlos Augusto Grabois; TEMPORÃO, 2018).

According to Bornemann (2021), Intellectual Capital (IC) is a convergent subject, especially in the recent decade, to various fields of importance to institutions such as organizational learning, innovation, and strategic organizational growth. The author also notes that IC management has supported business management by focusing on quality, process, and knowledge management in general, as well as Industry 4.0, which is crucial for studies in Science, Technology, and Innovation Institutes (BORNEMANN; ALWERT; WILL, 2021). The IC strategy can be also applied when dealing with health ecosystem growth and production. Given the importance of this notion, the European community has produced and adopted a declaration of IC that provides a clear connection between the production of value and the future (ALFIERO; BRESCHI; BERT, 2021). It is a technique for analyzing, developing, and reporting on an organization's intellectual capital, as well as system (ZICKGRAF, 2019).

IC has shown to be particularly useful in the development, production, and sale of a company's products and services because it covers a diverse area of knowledge. Because it is a powerful and comprehensive resource, a collective research tool was created to
carry out its implementation, the Intellectual Capital Statement (InCaS). The strategy has been used in small and medium-sized companies and has 5 core branches that aim to minimize complexity and implementation efforts (Figure 3). INCAS emphasizes a practical approach suitable for small companies, combining maximum benefit with unused innovation potential (ZICKGRAF, 2019).

**Figure 3.** The relationship between Intellectual Capital Statement (InCaS) structural model and Health Industrial Economic Complex (HIEC). The different elements of InCaS contribute to the overall knowledge and value creation within the HIEC, enriching and strengthens the overall health industrial complex.

In this scenario, it is important to consider the characteristics of each region. It can be stated that the absence of local recommendations and government funding contributes to and drives the implementation of partnership agreements and technology transfer licensing formed between universities and research centers with large pharmaceutical companies, seeking to constitute means for the development of their technological projects in the face of so many limitations and problems. In Brazil, for example, the advancement of science and technology occurs mainly in universities and public research centers like the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro and the Butantan Institute in São Paulo (ROSA et al., 2021) these centers played crucial roles during the pandemic after entering international partnerships and producing the AstraZeneca and Coronavac vaccines respectively.

Licensing through contracts transfers the right to use and commercialize the technology so that third parties can develop it independently, against payment of royalties (MARUGGI et al., 2019b). The contracts that make the technology available to the partners’ permission to use the intellectual properties, thus, consorting companies develop the final product using the same technology, decentralizing its production.

During the recent COVID-19 pandemic, this was commonly observed, where research centers and universities partnered with large companies for rapid vaccine production. A substantial increase in investment in research and development in several
countries was also observed (DE NEGRI; KOELLER, 2020) as was the deployment of international partnership agreements that enabled technology transfer to low and middle-income countries, making vaccines more accessible and cheaper. In short, the university sector contributes and actively participates in the production sector, transforming knowledge into solutions and benefits for society.

In this scenario, the "tripod" production model, which involves interactions between universities, industries, and government, has been recognized as fundamental for fostering innovation in low and middle-income countries. This model encourages collaboration, knowledge exchange, and technology transfer between these three pillars. By leveraging the expertise and resources of universities, the production capabilities of industries, and the support and regulatory frameworks provided by governments, countries can strengthen their health economic-industrial axis and enhance their capacity for large-scale vaccine production (MARIANO et al., [s. d.]).

In the context of Brazil, there have been contrasting data regarding the levels of scientific knowledge versus scientific and technological innovation generated during the pandemic. This highlights the need to foster stronger interactions and technology transfer between universities/research centers and the production sector, both public and private companies. By promoting these collaborations, Brazil can harness its scientific knowledge and transform it into practical solutions for the benefit of society. Strengthening the health-economic-industrial axis through such collaborations will not only contribute to vaccine production but also foster innovation and economic growth in the country (MARIANO et al., [s. d.]; SU; PENG; XIE, 2015).

Overall, the active participation of the university sector in the production sector, along with collaborative partnerships and technology transfer, has been instrumental in transforming knowledge into practical solutions, accelerating vaccine production, and generating societal benefits during the COVID-19 pandemic. Encouraging and strengthening these interactions will continue to be crucial for future vaccine development, as well as for addressing other health challenges and fostering innovation in low and middle-income countries.

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