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From COVID-19 to global health: challenges and opportunities in mRNA vaccine manufacturing

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Messenger RNA (mRNA) vaccines have emerged as a powerful tool in combating infectious diseases, including COVID-19, by synthesizing and delivering bioactive mRNA molecules that must remain stable and functional to transcribe target genes and effectively enter host cells. This review provides a brief examination of the synthesis and purification processes of mRNA vaccines, their formulation strategies, production scalability, regulatory frameworks, and global supply chain systems. Several challenges—including molecular instability during synthesis and lipid nanoparticle encapsulation, reliance on specialized equipment, insufficient supply of raw materials and skilled labor, and the need for standardized production quality at scale—are underscored. These concerns are further compounded by fragmented regulatory approval processes and the complexity of maintaining cold chain logistics, particularly in low-resource settings. Addressing these barriers is essential, and emerging solutions include integrating automation and artificial intelligence to enhance manufacturing efficiency and reduce associated costs. Additionally, ongoing research aims to improve the environmental stability of mRNA vaccines, thereby reducing reliance on cold storage and increasing accessibility in developing countries. Prospective developments further encompass the globalization of regulatory standards, the concentration of production capacities, and the application of mRNA technology beyond infectious diseases, including cancer and hereditary disorders. Overall, the review emphasizes that resolving manufacturing and logistical challenges together with international cooperation and supportive policy frameworks is crucial for advancing a new era of mRNA-based therapies accessible to populations worldwide.

KEYWORDS

mRNA vaccines, synthesis and purification, lipid nanoparticle delivery, cold chain logistics, manufacturing scalability

1 Introduction

Regarding immunization strategies, mRNA-based vaccines can be regarded as a significant breakthrough in the ongoing efforts to protect against viral diseases. Traditional vaccines typically contain a live or attenuated virus, an inactivated pathogen, or fragments of the pathogen. In contrast, mRNA vaccines function by delivering the genetic code required to produce a specific protein that elicits an immune response directly into cells. This novel mechanism not only extended the timeline for vaccine development but also provided a sufficiently flexible platform to accommodate new pathogens (1). This potential was demonstrated when the combined mRNA that proved effective in combating COVID-19 was developed. At the core of this recent advancement is the multiple-step manufacturing process associated with the production of mRNA vaccines. These steps include: the synthesis of high-purity mRNA, the encapsulation of mRNA into a lipid nanoparticle (LNP) carrier system, and the mitigation of the likelihood of adverse events. Each step encompasses distinct technical, logistical, analytical, and practical dimensions: these facets must integrate biochemistry, molecular biology, engineering, and regulatory science (2). The fundamental working mechanism of mRNA vaccines is depicted in Figure 1.

The knowledge that has emerged from the development of mRNA vaccines should not be studied or retained solely within the context of COVID-19 but should be applied globally. mRNA can facilitate the development of vaccines for various infectious diseases, including influenza, Zika virus, HIV, and others. Additionally, its potential as an oncological treatment and as a platform for targeted therapy has been explored; concurrently, employing mRNA in patient-specific therapies will depend on individual patient profiles (3). Nonetheless, this potential can only be realized when numerous critical constraints in the manufacturing process are addressed and resolved. Other noted advantages of mRNA technology include the capacity to rapidly produce booster doses, particularly during global emergencies (4). However, new challenges arise when devising solutions to satisfy the increasing global demand for a product already on the market, such as the availability of advanced equipment, adequate raw materials, and a sufficiently skilled workforce. Commending what may present difficulties involves ensuring a high-quality and safe product, while simultaneously adhering to the manufacturing standards stipulated by regulatory authorities (5).

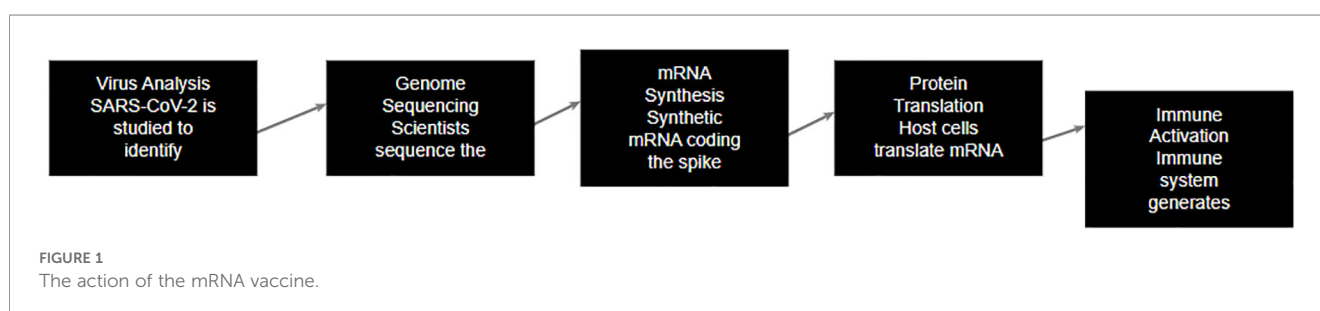
Some avenues for addressing these issues include implementing intelligent manufacturing, continuous manufacturing, and utilizing

artificial intelligence. These innovations may contribute to the development of more advanced mRNA vaccine production facilities by enhancing and optimizing processes for efficiency, quality, and economic viability (6). The principal factor is that mRNA vaccines can meet public health needs and potentially transform numerous medical specialties (7). However, for serialization to be effectively achieved, it is imperative to recognize that resolving the technical, logistical, and regulatory challenges related to the distribution and manufacturing of these products is essential. A broad spectrum of challenges continues to hinder mRNA vaccine development, ranging from production to delivery logistics, as shown in Figure 2.

Therefore, this review seeks to underscore these challenges and elucidate control measures for managing the complex dynamics associated with mRNA vaccines.

2 Inhibition and isolation of BPS mRNA synthesis

The first processes after mRNA creation are mRNA synthesis and mRNA purification. Each one of them has several technical and logistical issues. All of these questions should be solved when creating vaccines that use mRNA. An application of the *in vitro* transcription process is to generate a clean and constant mRNA molecule by replicating the genetic message of the DNA template. This step involves critical optimization of reaction conditions to obtain high yields of the desired functional mRNA, while minimizing interferences from short RNA bands and uncapped RNA (8). Slight differences in synthesis can radically change the activity and toxicity characteristics of the resulting substance. Acquiring the right DNA template is a limitation, as it involves RNA synthesis using T7 RNA polymerase. These reagents are costly, and all their activity has to be preserved – they become easily contaminated. Regarding the complete RNA, the IVT reaction, which yields high amounts, is relatively sensitive for controlling and monitoring, as it is a process that requires strong skills to operate (9). In essence, other characteristics, including magnesium ions, nucleotide, and temperature, are significant and quantified for *in vitro* transcription. Once RNA is synthesized, it gets capped to add a 5' capping required for the cell's lifespan and translation of the mRNA. The challenge of the technical problem is that if this cap structure is not perfect, the partially spine-capped mRNA may be less efficient in terms of functionality or may cause adverse immune reactions (10).





The other crucial step is purification, where the effects, including nucleotides, enzymes, double-stranded RNA, and other interferences that hinder successive synthesis, are abated. Other typical chromatography methodologies include ion exchange chromatography and size exclusion chromatography, but such processes are easier said than done when it comes to questions of scalability. Both must be optimized to obtain a linear, high-yield mRNA of high purity simultaneously, as its sequence is relatively sensitive and cannot be easily degraded (11). These difficulties increase with the translation of such a large amount of mRNA, especially during a pandemic. Some techniques that are useful for purifying bioactive compounds on a small scale may not be effective when scaled up; hence, they may not be suitable for large-scale applications. In addition, high cost per unit and easy availability of high-grade reagents and consumables are other stiff hurdles (12). Refining these problems in the synthesis of mRNA and subsequent purification is crucial for the further development of vaccine safety and efficacy, as well as for the scalability of the approach. The above challenges could be addressed through optimization of enzymatic reactions and improvements in the biochemical purification processes, as well as by developing improved production methods (13).

3 Formulation and stability: overcoming delivery hurdles

Two questions are most often asked concerning the formulation, development, and manufacturing of the mRNA vaccines: stability. As mentioned above, another step in translating the mRNA sequence into functional immunogenic molecules used in humans is the application of synthetically

produced mRNA into human cells. However, mRNAs are relatively unstable because they are prone to degradation by nucleases and changes in temperature and other conditions (14). However, another development challenge is manufacturing high-quality mRNA, synthesizing, purifying, and encapsulating it in a formulation that protects the mRNA from degradation while improving its biodistribution. As such, the main issue with the mRNA vaccines is what form the mRNA takes when encapsulated in the LNPs. Several of the LNPs employed for delivery additionally enable the uptake of the mRNA into host cells and enhance the protection of the mRNA from degradation. Structural and fundamental forms of LNPs, related to the encapsulation of mRNAs and their subsequent release into the body, are well represented by their structures and architecture (15). The LNPs need to be small enough to ensure that an early immune response cannot occur and neutralize the mRNA before it is internalized. The enhancement of the material's characteristics under study is a pressing issue and remains topical at the present stage.

The nature of lipid components incorporated into nanoparticles includes cationic lipids, phospholipids, cholesterol, and PEGylated lipids; the optimal concentration of these components must be achieved to ensure stability and function (16). The association of LNP has to be expandable to produce large batches at the same rate of equal convection and parity. Some challenges are noted during the formulation stage, specifically regarding the stability of the mRNA in the LNPs. The mRNA-LNP complex must remain stable at various temperatures for extended periods, as the transporting and storage conditions may not be ideal. This problem becomes particularly crucial during the COVID-19 pandemic, as the development of mRNA vaccines requires storage at low temperatures of -70°C (17). This was especially so where distribution and access presented implementation or practical challenges in delivering treatment in a low-resource context. In light of these challenges, researchers continually seek ways to enhance the thermal stability of mRNA-LNP formulations. This includes cryoprotectants, the ratio of mRNA to lipid in the nanoparticle formulation, and other delivery systems, such as polymers or lipids other than those currently used in the formulation (18). The idea is to generate mRNA vaccines that require comparatively less stringent storage conditions, since this would overcome some of the complexities of distribution worldwide, or at least the complex distribution to remote regions or rural areas.

Moreover, there is a need to generate stable mRNA vaccines capable of having a stable conformation to uphold resistance every time there is a change in humidity, temperature, and light exposure—the main aspects in stability analysis. The studies involve estimating the shelf life of the vaccines and additionally provide details concerning storage conditions and other treatments that the product requires (19). The FDA and the EMA, among other regulatory agencies, have established substantial regulations for stability testing, and manufacturers must comply with them when releasing a product. The issue of altering the specific mRNA sequence and the stability of the vaccines is connected to both the molecule and its delivery system. It is applied to introduce it into

cells (20). Overcoming these challenges entails refining the aspects of lipid formulation, including nanoparticle stability during storage and transportation, as well as other issues associated with scale-out and distribution. The concept of additional development will remain focused on the idea of mRNA vaccines for responding to various global problems of infectious diseases and other diseases; a significant problem arises regarding the formulation and stability of vaccines for large-scale usage (21).

4 Implementing measures to enhance supply in response to global market expansion

There are numerous challenges associated with scaling up the production of mRNA vaccines to meet global demand and address worldwide needs. Although the mRNA vaccines contain traits that can be easily manipulated and are effective in formulation, developing mRNA vaccines requires a substantial resource commitment for their production. This manufacturing transition from the small-scale production, as that which is done in the laboratory or pilot scale, to the industrial or commercial scale production is a factor that needs to be taken into consideration if there will be any possibility of producing these mRNA vaccines in significant quantities to meet the global demand, as was evidenced by the COVID-19 pandemic (22). The first difficulty manufacturers encounter when scaling up is the need for large-scale equipment and infrastructure. mRNA synthesis demands large bioreactors, strict temperature and pH regulation, and large-scale IVT equipment. The increasing demand for critical raw materials further underscores the need for resilient global supply chains, as

shown in Figure 3. Concerning the requirements for reproducing equipment for high-volume production, the issue of synthesizing large volumes of reagents, buffers, and raw materials must be addressed. Moreover, such equipment must be versatile enough to support any mRNA vaccine, as different products may require different synthesis procedures. Several considerations must be taken into account to achieve the desired yield when scaling the reaction from milliliters to hundred-liter levels (23).

Another problem organizations encounter when planning to increase productivity is the unavailability of raw materials. The production of mRNA vaccines requires additional materials, including nucleotides, plasmid DNA, and enzymes, which are known to be in limited supply. For instance, in the case of plasmid DNA used as the transcription template, only purified DNA with specific recommended quality characteristics should be used (24). Neglecting the procurement of these materials also affects production timelines, and in the long run, prices can skyrocket. Geographically, the sources of these raw materials are global; therefore, disruptions anywhere in the world can affect vaccine production. To produce and operate machinery in large quantities of a given product, it is necessary to ensure adequate stocks of these materials. Loss of jobs and lack of skills additionally present other core challenges to increasing the production of mRNA vaccines (25). This is attributable to several reasons. Firstly, those who write the products are well-trained individuals who have studied molecular biology, biochemistry, and engineering in manufacturing. This has been another major setback, occasioned by the rapid increase in the production of mRNA vaccines that lack adequate human capital. To overcome this problem, more funds should be invested, first and foremost, in training new personnel, both by companies and governments. Substitute technology:



FIGURE 3
Raw material market size for Global mRNA synthesis.

They also assist in managing the scarcity of skilled and unskilled workers, as it offers a chance to eliminate several instances of manual labor associated with continuous, mechanical, and patterned processes (26).

Another operational factor, which has become more paramount as manufacturers move from original production to mass production, is the quality of the mRNA vaccines. However, when production increases in volume, the variability in product quality also rises. It becomes challenging to ensure that every batch manufactured meets the criteria, and doing so at a large scale is almost impossible (27). Here, it is mandatory to establish high levels of quality assurance and simultaneously utilize analytical chemistry applications to identify possible contamination, as well as to determine the stability of the mRNA molecules and other formulation characteristics. Preliminary real-time monitors, including PAT and other sophisticated monitoring devices, help an organization identify potential issues that may arise in the early stages of manufacturing. Furthermore, manufacturing capacity must be responsive to global market needs within a short timeframe (28). For instance, when COVID-19 erupted, mRNA vaccines had the noble task of manufacturing billions of doses quickly. Although through AM, the volatile demand, notwithstanding, has been met adequately, production in the traditional manufacturing setting could never have coped with such a spillover of demand due to flow turbulence. To avoid such pitfalls in the future, manufacturers are investing heavily in the development and construction of modular and flexible plants that can be easily adapted to produce any vaccines as deemed necessary due to the threat posed by any disease (29).

Others are regulations, while increasing the production of mRNA vaccines to meet the demand from another challenge that must be met. At this point, there were nods of acceptance that vaccine manufacturers have specific regulatory requirements imposed by agencies, including the U.S. FDA and EMA (30). When production increases, it becomes tough to stick to such regulations later. Each facility requires an inspection, and numerous records must be provided to demonstrate that the manufacturing process complies with the health authority's requirements regarding safety, effectiveness, and quality. Of course, such rules still help minimize risks associated with the activities of technological companies. Still, such restrictions impose limitations on the ramp-up process in new markets and niches (31). Moving from producing central mRNA vaccines means that issues concerning infrastructure, materials and components, human resources and workforce cadre, dimensional requirements, quality control, and compliance with global market regulations become pertinent. These challenges, nevertheless, are not far from being tackled (32). Thus, further bolstering research in technology and the workforce in the creation of mRNA vaccines, it is relatively easy to produce a larger number of doses for any vaccine, and at an affordable cost for many. These advantages of the rapidly developed and delivered COVID-19 vaccines should be retained for the next public health emergency and to expand the usage of mRNA in worldwide medical services (33).

5 Navigating regulatory complexities and supply chain limitations in the advancement of mRNA vaccines

Two of the challenges associated with developing and deploying mRNA vaccines are regulatory and supply-chain related. These difficulties are further compounded by the need to respond rapidly during crises with appropriate products and by the inherent complexity of the emerging mRNA technology. A critical balance in meeting all regulatory requirements for mRNA vaccines lies in accomplishing this without disrupting the supply chain, which is crucial in ensuring the global distribution of vaccines (34). The initial obstacle in synthesizing mRNA vaccines is the regulatory landscape, which is subject to ongoing updates and varies according to different authorities, starting with national bodies such as the FDA and EMA, and extending to international organizations like the WHO. These agencies dedicate time and resources to ensuring that vaccines are safe, effective, and produced using high-quality materials and processes. Nevertheless, the mRNA platform remains relatively novel within the global pharmaceutical market, and for an extended period, such products had not been developed (35).

This typically includes pre-clinical studies, clinical trials, and the submission of timelines and other relevant documents that demonstrate the vaccine's safety, efficacy, and quality. There are additional complexities associated with mRNA vaccines, including ensuring that the encapsulated lipid nanoparticles (LNPs) are non-toxic and do not elicit adverse immune responses (36). These actions could slow the development of production procedures related to the vaccines and their distribution, especially where uptake is rapid. Although requests for more rapid approval mechanisms, such as EUAs, during calamities are valuable, they present unknowns and additional burdens to manufacturers (37). Moreover, standards differ from country to country; therefore, a product approved for production and manufacture in one region may take a considerable amount of time or even skip the approval process altogether in another area. These problems would be solved to the extent that distilling regulatory standards, along with developing international mechanisms for vaccine approval, is an outstanding achievement (38). First of all, organizing the supply chain of mRNA vaccines is rather intricate in itself, as it involves factors necessary for production, specialized equipment, and other aspects related to the transportation of the vaccines. Creating the mRNA vaccines, particularly the synthesis of the vaccines, involves using high-purity materials, including nucleotides, enzymes, plasmid DNA, and lipids, for nanoparticle construction (39). Such significant inputs can be complicated to source or delay delivery, a situation that is experienced especially when there is an influx of orders, as was witnessed with the COVID-19 vaccines. Moreover, the distribution of mRNA vaccines is also an issue in some way. For example, the Pfizer-BioNTech vaccines must be stored and transported at extremely low temperatures, which limits distribution and the cold chain, especially in low-income or specific locations with limited facilities and transportation. This implies that

an appropriate supply system should be in place to prevent vaccine expiration during transit or while waiting for optimal storage conditions to be established (40).

Considerations, including political and/or economic factors such as trade restrictions, geopolitics, and the availability of biological transport, should be taken to eliminate any factors that cause delays. For instance, restrictions on movement, such as factory lockdowns, border closures, and limitations on the number of spaces available to ship vaccines, were implemented during the COVID-19 pandemic (41). This paper highlights that one of the major concerns is how regulatory hurdles and supply chain factors hinder the timely and optimal manufacturing and distribution of mRNA vaccines. Organizing efforts to simplify regulation, a robust supply chain, and building relationships are necessary to address those challenges. Eliminating these bottlenecks enables more people to be vaccinated immediately, with mRNA vaccines being a viable shield against global health challenges (42). Furthermore

6 Future directions toward innovations and strategic solutions

The future of manufacturing mRNA vaccines is promising, as ongoing research continues and strategic solutions to existing challenges are being refined. While the mRNA used for COVID-19 vaccine development is still under development, the breakthrough has many more implications for the future, including the creation of vaccines for various types of viral infections and treatments for cancer, genetic diseases, and other diseases. The way ahead is marked by significant challenges, including production improvement and scale-up, compliance and registration, and delivery across the international environment (43). There are numerous opportunities to accelerate the production of mRNA vaccines, including the application of innovative technologies such as automation, artificial intelligence, and continuous manufacturing. It has also begun reducing the dependence on human operators, thereby minimizing the possibility of errors, deviations from standards, and slower work rates. Some steps that can be readily automated include Quality assurance, mRNA synthesis, and packaging within LNPs. Automation also minimizes labor use and accelerates the expansion of production capabilities, ensuring that the international immunization program's needs can be met (44).

Another unused concept innovation area is continuous manufacturing. It is quite different from the standard batch production type, which prolongs the duration of mRNA vaccine production and increases production costs. This approach features a continuous and smooth flow of materials and processes, with real-time control and optimization, resulting in efficient and consistently high-quality products. With continuous manufacturing, companies can quickly supply more mRNA vaccines while achieving increased purity and utilizing fewer resources (45). This could lead to a significant change in how vaccines are manufactured and administered, particularly during pandemics. Similarly, AI and

machine learning are likely to help improve the efficiency of mRNA vaccine production. These technologies can be applied in forecasting and enhancing production processes, as well as in determining the critical flow rates and/or designing improved mRNA sequences or lipid nanoparticle formulations. They could also use machine learning to identify potential issues in the production process and recommend changes that would enhance yield, quality, and reliability, thereby accelerating vaccine manufacture (46, 47).

Artificial intelligence and machine learning are likely to play a central role in making such distributed mRNA manufacturing networks technically and economically sustainable (48). At the design stage, supervised and generative models trained on experimental datasets that link mRNA sequence features and lipid nanoparticle compositions to expression, immunogenicity, and toxicity can help identify constructs with better performance than manual trial-and-error approaches (49). These models can draw on public sequence repositories (e.g., viral and host genomes, protein databases) and in-house experimental data. Although model training may require access to GPU resources, routine design tasks can usually be integrated into existing computational infrastructure without incurring prohibitive costs.

Along the production line, AI can support optimization of *in vitro* transcription, purification, and formulation by analyzing process analytical data from reactors, chromatography systems, and electronic batch records (50). Techniques such as Bayesian optimization, multivariate regression, and time-series modeling can suggest improved conditions for enzyme concentrations, reaction times, column parameters, and mixing ratios, thereby increasing yield and purity while reducing variability and waste. In parallel, machine-learning-based anomaly detection and real-time monitoring can enhance quality control, which is essential when scaling from laboratory to industrial production and when operating continuous manufacturing systems (48).

At the level of entire facilities and supply chains, integrating AI with automation and continuous manufacturing creates opportunities for predictive maintenance, dynamic production scheduling, and optimized cold-chain logistics (51). Models built on equipment performance data, demand forecasts, and transportation constraints can help minimize downtime, anticipate shortages of critical raw materials, and allocate limited low-temperature storage capacity more efficiently, particularly in regional centers in low- and middle-income countries. These applications primarily run on standard CPU-based industrial data platforms and manufacturing execution systems, enabling gradual improvements in efficiency and reliability without necessitating a complete redesign of existing plants.

Despite these technological opportunities, the future trajectory of mRNA vaccines is shaped by broader economic and political dynamics. Recent U.S. funding cuts, together with the continued dominance of live attenuated and protein subunit vaccines in many low- and middle-income countries, have understandably raised doubts among investors and policymakers about the near-term commercial prospects of mRNA platforms (52). At the same time, the global clinical pipeline of mRNA candidates has expanded

beyond COVID-19 to include vaccines and therapeutics for influenza, RSV, HIV, tuberculosis, dengue, and multiple cancer indications (53). Recent analyses suggest that the majority of active mRNA vaccine trials now target non-COVID-19 diseases. In parallel, initiatives such as the WHO mRNA Technology Transfer Programme and regional hubs in Africa, Latin America, and Asia aim to build sustainable local manufacturing capacity and skilled human capital in low- and middle-income countries, reducing reliance on a few producers in high-income regions (54). If these efforts are coupled with advances in thermostable formulations, automation, AI-driven process optimization, and innovative financing mechanisms, mRNA vaccines could become increasingly attractive for national immunization programs and private investors, even in resource-constrained settings.

Logistical challenges will remain a crucial consideration integral to the long-term success of vaccination with mRNA vaccines; stability and formulation of mRNA vaccines will be critical. Another approach is to increase the thermal stability of an mRNA-LNP formulation. Still, more work is being done to develop new stabilizers and lipid formulations that can encapsulate the mRNA to sustain the heat shock while maintaining viability at more moderate storage and transport temperatures (55). For example, improvements in cryoprotectants, polymers, and lipid content can increase the storage temperature of mRNA vaccines to conditions other than

the ultra-low temperatures currently required, thereby helping to remove a significant barrier in delivering vaccines to developing countries and areas with less sophisticated infrastructure and transportation. Additionally, new technologies, including dry formulations that eliminate the need for a cold chain, could facilitate the global expansion of mRNA. Under these types of dry formulations, several costs associated with maintaining the cold chain would be significantly reduced, including the Hardship related to administering vaccines to remote regions where ultra-cold facilities are scarce (56). Beyond infectious diseases, mRNA vaccines are being explored for oncological applications, as illustrated in the emerging therapeutic frontiers, as shown in Figure 4.

The COVID-19 mRNA vaccines must additionally be scaled up and distributed worldwide; this is why supply chain development is needed. One is expected to focus on the construction of more global production facilities; however, this is currently limited to specific regions, particularly the LMICs. Such facilities may reduce the degree of reliance on large manufacturing centers and may also increase equality in terms of dose distribution (57). Moreover, such production sites would decrease transportation and storage expenses, solve the problem of supply chain constriction, and avoid the consequences of geopolitical instability. Government collaboration with other governments, international agencies, and companies could help support these localized production factories,

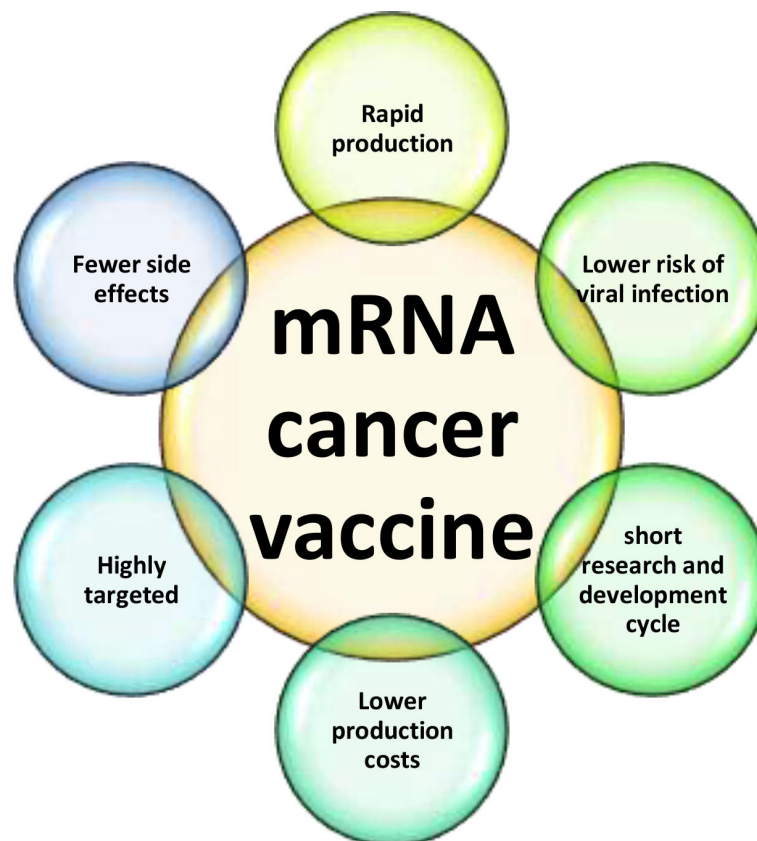


FIGURE 4
Recent frontiers of mRNA cancer vaccine.

in BARDA-funded mRNA vaccine development contracts, covering 22 projects across respiratory and other infectious diseases, and announced that no new federally backed mRNA vaccine projects would be initiated in the near term (64). Public health experts have warned that these cuts will slow platform innovation, weaken preparedness for future pandemics, and may prompt companies, manufacturing facilities, and skilled personnel to relocate to regions that offer a more stable and supportive policy environment. This development highlights the importance of diversifying leadership in mRNA vaccine research and manufacturing, as well as building resilient, globally distributed capacities that are not overly dependent on a single country.

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global clinical pipeline of mRNA candidates is expanding to include influenza, RSV, HIV, tuberculosis, oncology, and rare diseases. Multiple regions are investing in regional manufacturing hubs and technology-transfer initiatives that could reduce reliance on a small number of producers. If these efforts are coupled with advances in thermostable formulations, automation, AI-driven process optimization, and supportive financing mechanisms, mRNA vaccines could become progressively more attractive for national immunization programs and for investors, including in resource-constrained settings.

7 Conclusions

Developing mRNA vaccines has provided vaccine scientists with unprecedented means to produce low-cost and highly effective vaccines to address global infectious diseases within a shorter timeframe. However, the transition from laboratory-scale production to the worldwide distribution of this technology has encountered numerous challenges and constraints that must be addressed to realize the platform's full potential. This review has focused on mRNA synthesis and purification, mRNA formulation, scale-up, and other regulatory and supply chain challenges that are essential for producing mRNA vaccines safely, effectively, and at scale. Synthesizing and purifying mRNA is a notably sensitive process that requires precise and high-quality reagents. These processes demand careful optimization to ensure high yields and product purity while minimizing contamination risks. Additionally, the concept of mRNA itself—particularly the encapsulation of mRNA into lipid nanoparticles—presents unique challenges associated with stability and delivery. Lipid nanoparticle technology must continue to evolve rapidly, particularly as thermal stability remains a concern, offering opportunities to overcome these barriers and make vaccines more storable and transportable.

Perhaps the most significant challenge is scaling up production to meet international demand, which requires substantial investment in machinery and equipment, reliable sourcing of raw materials, and the development of a skilled workforce, given the capital-intensive nature of the production process. The COVID-19 pandemic has demonstrated that conventional, rigid industrial systems must be restructured to become more adaptable, and that steady advances, such as automation, continuous production, and real-time monitoring, significantly reduce bottlenecks. Likewise, securing the availability of raw materials and diversifying supply chains will be instrumental in enhancing vaccine production. Further complexity arises from regulatory and supply chain issues. For this reason, regulatory agencies must adapt; mRNA vaccines represent a novel platform, warranting streamlined approval processes to expedite patient access to these therapeutic innovations. Concurrently, it is imperative to bolster global distribution capacities, operating continuously in a connected world, while minimizing geopolitical and other barriers to ensure equitable access to mRNA vaccines worldwide. The continued advancement of mRNA technology, which has so far shown early promise in combating infectious diseases, is anticipated to be profoundly transformative. Emerging improvements in the manufacturing, formulation, and regulatory

processes for mRNA vaccines and therapies will strengthen existing supply chains. However, realizing this potential will require sustained political commitment and investment across multiple regions, particularly as some major funders scale back infectious-disease mRNA programs. At the same time, other countries and multilateral initiatives move to develop their own manufacturing hubs and regulatory frameworks. When these challenges are addressed and international collaboration is fostered, the world will usher in a new era of medicine, leveraging mRNA technology to combat future global health threats more effectively.

Author contributions

VC: Conceptualization, Writing – review & editing, Writing – original draft, Methodology. AM: Resources, Writing – review & editing, Methodology. MN: Data curation, Writing – review & editing, Conceptualization. AS: Investigation, Writing – review & editing, PD: Writing – review & editing, Resources, Investigation. UN: Resources, Writing – review & editing, AS: Supervision, Writing – review & editing, Conceptualization, Validation, Writing – original draft, Visualization.

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