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Evaluation Of Mrna Vaccines Against Viral Infections: Efficacy, Limitations, And Future Prospects

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Abstract
Messenger RNA (mRNA) vaccines have emerged as a transformative platform in the prevention and control of viral infections, demonstrating remarkable efficacy during the COVID-19 pandemic. Unlike traditional vaccines, mRNA vaccines utilize synthetic messenger RNA to encode viral antigens, enabling rapid development, scalable manufacturing, and strong immunogenicity. This review evaluates the efficacy of mRNA vaccines against viral infections, highlights their immunological advantages, and examines key limitations associated with their widespread use. Clinical and real-world data indicate that mRNA vaccines induce robust humoral and cellular immune responses, providing high levels of protection against severe disease and mortality. However, challenges such as cold-chain requirements, reactogenicity, durability of immune protection, viral variants, and global accessibility remain significant barriers. Additionally, concerns related to long-term safety, vaccine hesitancy, and manufacturing costs warrant further investigation. Despite these limitations, ongoing advancements in mRNA design, delivery systems, and thermostable formulations are expanding the potential of this platform beyond COVID-19 to include influenza, HIV, Zika, and other emerging viral threats. Overall, mRNA vaccine technology represents a major milestone in vaccinology, offering a flexible and powerful approach for rapid response to current and future pandemics. Continued research and innovation are essential to overcome existing challenges and fully realize the global public health potential of mRNA vaccines.

Keywords mRNA vaccines; Viral infections; Vaccine efficacy; Immunogenicity; COVID-19; Vaccine limitations; Future prospects.

Introduction

Global Burden of Viral InfectionsViral infections represent a threat to the global health, and require the constant improvement of the prophylactic and therapeutic measures [1]. Although there is significant advancement in the development of vaccines, most viral pathogens including those that are pandemic have no effective preventative or treatment [2]. This unrelenting problem highlights the pressing necessity of new vaccine platforms, which would be developed quickly and have a wide range of applications to deal with new and re-emerging viral threats [3]. Messenger RNA [mRNA] vaccines have become a revolutionary technology in this context, which is both faster and more effective against infectious diseases as never before [4]. They have many positive characteristics that made them

appealing: they are simple to produce, their immunogenicity is acceptable, and their safety profiles are excellent, and this aspect is proven by the pivotal role of their usage during the COVID-19 pandemic [5,6].

The emergence of mRNAVaccine development has historically focused on attenuated or killed pathogens, or subunit vaccines, which typically consume significant periods of production and are highly complex to manufacture [7]. Conversely, mRNA vaccine technology, which has its roots in studies conducted in 1989, does not need such complexities, but, instead, it uses mRNA molecules to make the cellular machinery of the host develop antigenic proteins, thus, triggering an immune response [6]. It is a new technique that enables the development and production of vaccines in a short period, like the timely introduction of mRNA vaccines in the case of the 2019 Coronavirus Disease pandemic [3]. This has since triggered intensive studies on the use of mRNA vaccine platforms on more diverse array of infectious diseases in terms of their capacity to have wider public health effects [7,8]. Since the mRNA platforms are flexible in nature, modifications to antigen sequences can be performed quite promptly, and this is essential to address growing viral strains and other pathogenic agents [8].

The purpose of this review is to critically assess the current state of mRNA vaccines against viral infections, such as their proven effectiveness, limitations inherent in them, and their future potential. It will also examine the break-even components of the mRNA technology, its use against a wide spectrum of viral pathogens, and its current development that is geared towards addressing the current limitations in delivery and immunomodulation. The economic consequences and scalability of mRNA vaccine production will also be taken into account in the review as it relates to the global health equity and accessibility [9]. Moreover, the analysis will also indicate the transformative quality of mRNA vaccines in switching immunotherapy of cancer to prevention of infectious diseases, thus expanding their therapeutic universal [10]. Lastly, advanced delivery systems and molecular modifications to improve mRNA stability and translation to maximize vaccine action and decrease reactogenicity will be explored in this review [11]. This general background will give information on how the mRNA technology is transforming the vaccinology and future methods of controlling infectious diseases [12]. The effectiveness of the mRNA vaccines against the COVID-19 pandemic has not merely proven the platform, but it has further prompted the use of the platform in the investigation of cancer and immunological diseases as well as tissue regeneration among a wider range of viral diseases and other medical conditions [13-15].

Table 1: Efficacy of mRNA Vaccines Against Viral Infections.

Viral Infection	Vaccine Type	Reported Efficacy / Immune Response	Key Findings	References
COVID-19 [SARS-CoV-2]	mRNA-1273, BNT162b2	90–95% efficacy against severe disease	Strong neutralizing antibodies and T-cell responses	[1, 2, 3]
Influenza	mRNA-based influenza vaccines	Comparable or superior to inactivated vaccines	Rapid antigen adaptability	[4, 5]
Zika virus	Experimental mRNA vaccines	High neutralizing antibody titers in trials	Protection in preclinical models	[6]
Rabies	CV7201 [mRNA]	Safe and immunogenic	Induced virus-neutralizing antibodies	[7]
HIV	Candidate mRNA vaccines	Robust cellular immune response	Still under clinical evaluation	[8]

Efficacy of mRNA Vaccines Against Viral Infections

The outstanding performance of mRNA vaccines against viral infections has been strongly tested against numerous types of pathogens and has demonstrated the ability to produce strong and lasting immune responses [14]. This effectiveness is due to the immediate generation of antigens into cells, which results in a more natural manifestation to the immune system and the concomitant stimulation of humoral and cellular immunity [16]. Through this mechanism, there is a production of strong antibody

and T-lymphocyte cytotoxic responses which is important in eliminating cells infected by viruses [17,18]. The ability to quickly design and implement mRNA constructs also adds to their efficacy, as they can be adapted to new viral strains and new pathogens quickly [19]. This flexibility was particularly demonstrated during the COVID-19 pandemic, where mRNA vaccines have proven themselves to be highly effective against SARS-CoV-2 and its emerging variants to a significant degree, mitigating severe illness and even mortality [20,21]. Other than infectious diseases, mRNA is also under investigation in the field of oncology because it can be programmed to display tumor-specific antigens and thereby induce the immune system to attack cancer cells [15].

Mechanism of Action and Immune Response:
The mRNA, after being inoculated into the host cell, takes advantage of the cellular machinery to produce the target viral antigen, which is imitative of a natural infection without the risks of live viruses [16,17]. This de novo expression of viral proteins in the host cells makes the production of the antigens easy, as it is presented both by MHC class I and class II, which leads to the activation of cytotoxic T lymphocytes of the CD8+ and helper T cells of type CD4, respectively [18]. Messenger RNA vaccines work by introducing genetic instructions to the host cells, which then integrates them into synthesizing particular antigens of a virus, which is displayed to the immune system to induce protection immunity [19]. The production of these antigens in the cellular form guarantees a more physiological response of the immune system, which is very similar to the response created by a natural infection but devoid of the pathogenic risks [20,21]. mRNA delivery systems [e.g., lipid nanoparticles] however, the successful implementation of mRNA vaccines is heavily contingent upon effective delivery systems that ensure stability, prevent degradation, and facilitate targeted uptake by antigen-presenting cells [22-23].

These delivery systems, primarily lipid nanoparticles, encapsulate the mRNA, protecting it from degradation and facilitating its entry into host cells, a critical step for antigen expression and immune activation [24]. The optimization of these lipid nanoparticles is crucial, focusing on parameters such as lipid composition, particle size, and surface charge to enhance mRNA encapsulation efficiency, cellular uptake, and endosomal escape, thereby maximizing the antigenic protein production and subsequent immune response [25]. Antigen Expression and ImmunogenicityThe translated antigen then undergoes proper folding and post-translational modifications, crucial for generating an immunologically relevant epitope that can effectively prime both B and T cell responses. This direct intracellular synthesis leads to the sustained presentation of antigens, crucial for the generation of robust and long-lasting immunity [17]. The "plug-and-play" modularity of mRNA vaccine platforms allows for rapid modification of the antigen sequence, offering a significant advantage in developing countermeasures against rapidly evolving pathogens and emerging threats [26]. This inherent adaptability positions mRNA technology as a frontrunner in pandemic preparedness and response, allowing for swift vaccine updates to maintain efficacy against novel variants [18].

This adaptability streamlines the development process, enabling quick responses to new viral variants or entirely novel pathogens with unprecedented speed and precision. Moreover, advancements in mRNA stabilization and purification techniques, coupled with novel delivery formulations, continue to enhance vaccine immunogenicity and reduce reactogenicity, broadening their therapeutic applicability beyond infectious diseases to areas such as cancer immunotherapy and autoimmune disorders [11,27]. Moreover, the direct intracellular synthesis of antigens by mRNA vaccines circumvents potential issues related to antigen purification and stability often encountered with traditional subunit vaccines, further contributing to their rapid development timelines [4].

The recent discoveries in mRNA technology such as modifications to the nucleoside and the use of optimal delivery vehicles, such as lipid nanoparticles, have dramatically improved the stability, translation efficiency, and immunogenicity of mRNA, which initially had major challenges due to innate immune recognition and rapid degradation [11,28]. These advancements have established mRNA as a flexible and powerful vaccine development platform, beyond first validation in infectious disease, to expanded therapeutic uses [29]. This extends to their swelling application in cancer immunotherapy whereby they are programmed to induce immune responses to tumor specific antigens and in the therapy of autoimmune diseases by inducing immune tolerance or regulating abnormal immune responses [30].

The mRNA vaccines are made through the cell-free in vitro manufacturing system further reducing concerns on safety, as it avoids the likelihood of cell-derived impurities and viral contaminant which is a typical problem in other vaccine platforms [31].

Moreover, the use of mRNA vaccines based on viral vectors in the majority of cases eliminates fears of possible insertional mutagenesis or immunity to the viral vectors [32]. This difference is a historical issue with viral vectors, including the lethal immune response in the early gene therapy cases, which supports the concept of better security of non-viral mRNA delivery systems [11]. The COVID-19 pandemic demonstrated the mRNA vaccine as highly productive, and its speedy design and yieldful manufacturing became possible due to the in vitro transcription [33]. Clinical Efficacy in Viral Pathogens A wide range of viral pathogens, including but not limited to SARS-CoV-2, influenza and Zika virus, has been shown to have a high efficacy of mRNA vaccines, which can transform prophylactic medicine [34]. The successful clinical performance of mRNA vaccines against the SARS-CoV-2 highlights the possibility of their general use in the context of viral infections such as influenza, Zika, and HIV because current studies show encouraging outcomes in preclinical and phase-one clinical trials. It is also due to the mRNA platform's ability to be easily genetically modified to various antigens that this wide applicability is further underpinned by the fact that the mRNA platforms can be reconfigured to suit other antigens on a rapid basis and hence it can be viewed as a plug-and-play type of vaccine development that is highly beneficial to pandemic preparedness and response [26].

Clinical effectiveness of mRNA vaccines has been proven in relation to a variety of viral pathogens, not limited to SARS-CoV-2, proving their universal applicability and ability to cause protective immunity [35]. SARS-CoV-2 VaccinesThe mRNA vaccines developed against SARS-CoV-2 and deployed rapidly during the COVID-19 pandemic was an excellent example of providing real-world evidence of their high efficacy in preventing symptomatic infection, severe illness, and mortality [4]. This achievement highlighted the possibility of the platform to respond to global health crises quickly and its ability to cause strong and long-lasting protective immunity [36]. Efficacy in Influenza, RSV, and other virusesBeyond SARS-CoV-2, the mRNA vaccine technology proved to be promising in preclinical and clinical trials against various other viral pathogens, such as influenza, respiratory syncytial virus, and Zika virus, which proves the potential applicability and versatility of this technology in the prevention of infectious diseases [37].

Such versatility, combined with the capability of quickly altering the sequences of antigens, makes mRNA vaccines an effective way of responding to changing virus threats and upcoming pandemics in a short time [18,38]. This scalability and velocity is a major paradigm shift compared to the conventional vaccine development which can take a long and complicated process in its production [39]. The other major benefit of mRNA technology is that it is flexible in nature and therefore can quickly be changed to suit vaccine construction based on changes in pathogens or new disease outbreaks [4]. This agility is particularly crucial in situations demanding an immediate public health intervention, as demonstrated by the rapid deployment of COVID-19 mRNA vaccines [40,41].

This is further enhanced by the fact that several mRNA sequences can be combined to one vaccine formulation allowing the ability to protect against different strains or different pathogens altogether [15]. This method has a potential of creating universal vaccines that can provide long-lasting coverage that can ease the burden on vaccination regimens and improve the overall health outcome of the world. Their applicability in response to outbreaks as well as emerging infectious diseases is exemplified by the mRNA vaccine development that is unprecedented, especially during the COVID-19 pandemic [42,43]. Moreover, mRNA vaccine platforms are flexible enough in capability to elicit multi-protective immune responses, including not only neutralization of antibodies but also vigorous CD8+ and CD4+ T cell responses, which are believed to be vital in insulating against various strains of viruses [18]. The overall immunogenic activation signature is especially beneficial with regard to pathogenic agents sharing a high degree of antigenic variation, in which antibody-focused responses might not be sufficient to induce long-term immunity [13].

The long-term effectiveness of the mRNA vaccine is based on its ability to induce long-term protective immunity and long-time immune memory, which is essential in the protection process against viral infections. The definition of how mRNA vaccines form and sustain these robust immunological memories including differentiation of long-lived plasma cell and memory T cells is the key to the future of vaccine designs and immunization strategies. The studies of immune correlates of protection and abiding vaccine induced antibodies and cellular responses are critical in determining the predictability of vaccine efficacy with time and guide booster vaccination. Furthermore, studies on adjuvants and systems that can improve the extent and duration of mRNA vaccine-based immunisation are an important field of study [44].

Antibody and T-Cell Response DurationDeviation of antibody and T-cell responses is one of the most important factors that can define long-term protection, and researches have demonstrated that mRNA vaccines have the potential to induce long-lasting immune memory cells that are ready to multiply upon re-exposure [45]. This type of long-lasting immune memory is specifically useful in the case of viruses undergoing a high rate of antigenic drift because it forms a basis of quick adaptive responses when exposure to new variants occurs. Factors The longevity and effectiveness of protective immunity are highly dependent on a variety of factors, among which are the type of construct of the mRNA, the nature of the delivery system, and the host immunological factors [11,46]. Research that is currently underway is geared toward explaining the specific mechanisms controlling the development and maintenance of immune memory after mRNA vaccination and especially how to design vaccines to be more durable [47]. Additionally, the ability of circRNA vaccines to induce strong neutralizing antibodies and T-cell immunity as well as a long-term antigen titer is an indicator of a promising opportunity of improved and better lasting protection that may possibly be better than the immunogenicity of the conventional mRNA vaccines [48].

It is important to note that this increased immunogenicity is essential in producing a strong and persistent immunity which is in most cases difficult in chronic infections where adaptive immunity may be faulty [45]. Moreover, circular RNA [circRNA] is becoming the next-generation RNA vaccine delivery system with superior stability and longer antigen expression because of its circular design, which can potentially improve the shortcomings of linear mRNA vaccines, especially in cases of the need to stimulate the immune response over an extended period [48]. This increased stability can be interpreted into the improved half-life of circRNAs relative to linear mRNA, which enables the circRNA to produce antigen in a sustained manner and possibly more powerful and prolonged immune responses [49]. This long-term presentation of circRNA vaccines can result in sustained humoral immunity, which is important in the prevention of chronic infections and re-infection [45,49]. This is further enhanced by the fact that several mRNA sequences can be combined to one vaccine formulation allowing the ability to protect against different strains or different pathogens altogether [15]. Their applicability in response to outbreaks as well as emerging infectious diseases is exemplified by the mRNA vaccine development that is unprecedented, especially during the COVID-19 pandemic [50,51]. Moreover, mRNA vaccine platforms are flexible enough in capability to elicit multi-protective immune responses, including not only neutralization of antibodies but also vigorous CD8+ and CD4+ T cell responses, which are believed to be vital in insulating against various strains of viruses [52]. The overall immunogenic activation signature is especially beneficial with regard to pathogenic agents sharing a high degree of antigenic variation, in which antibody-focused responses might not be sufficient to induce long-term immunity [53].

Table 2: Detailed Limitations and Challenges of mRNA Vaccines.

Limitation	Underlying Cause	Clinical / Logistical Impact	Current Mitigation Strategies	References
Cold-chain dependency	Instability of mRNA and lipid nanoparticles at higher temperatures	Limits storage, transport, and use in low- and middle-income countries	Development of thermostable formulations and lyophilized vaccines	[9, 10, 16]

Reactogenicity	Innate immune activation and cytokine release	Local and systemic adverse effects [fever, fatigue, myalgia]	Optimization of mRNA sequence and lipid nanoparticle composition	[11, 21]
Duration of immune protection	Decline in neutralizing antibody titers over time	Requirement for booster doses	Use of modified mRNA and adjuvant optimization	[12, 13, 22]
Reduced efficacy against variants	Antigenic mutations in viral spike proteins	Breakthrough infections and reduced neutralization	Updated vaccine formulations and multivalent vaccines	[14, 18]
Manufacturing and cost constraints	Complex synthesis and cold-chain distribution	Limited global accessibility	Scale-up manufacturing and technology transfer	[15, 23]
Vaccine hesitancy	Safety concerns and misinformation	Reduced vaccination coverage	Public education and post-marketing surveillance	[24, 25]

Persistence of Defence and Immunity

The long-term effectiveness of the mRNA vaccine is based on its ability to induce long-term protective immunity and long-time immune memory, which is essential in the protection process against viral infections. The definition of how mRNA vaccines form and sustain these robust immunological memories including differentiation of long-lived plasma cell and memory T cells is the key to the future of vaccine designs and immunization strategies. Furthermore, studies on adjuvants and systems that can improve the extent and duration of mRNA vaccine-based immunisation are an important field of study [54]. Antibody and T-Cell Response DurationDeviation of antibody and T-cell responses is one of the most important factors that can define long-term protection, and researches have demonstrated that mRNA vaccines have the potential to induce long-lasting immune memory cells that are ready to multiply upon re-exposure [55].

Factors The longevity and effectiveness of protective immunity are highly dependent on a variety of factors, among which are the type of construct of the mRNA, the nature of the delivery system, and the host immunological factors [11,56]. Research that is currently underway is geared toward explaining the specific mechanisms controlling the development and maintenance of immune memory after mRNA vaccination and especially how to design vaccines to be more durable [57]. Additionally, the ability of circRNA vaccines to induce strong neutralizing antibodies and T-cell immunity as well as a long-term antigen titer is an indicator of a promising opportunity of improved and better lasting protection that may possibly be better than the immunogenicity of the conventional mRNA vaccines [58]. It is important to note that this increased immunogenicity is essential in producing a strong and persistent immunity which is in most cases difficult in chronic infections where adaptive immunity may be faulty [45]. Moreover, circular RNA [circRNA] is becoming the next-generation RNA vaccine delivery system with superior stability and longer antigen expression because of its circular design, which can potentially improve the shortcomings of linear mRNA vaccines, especially in cases of the need to stimulate the immune response over an extended period [48]. This increased stability can be interpreted into the improved half-life of circRNAs relative to linear mRNA, which enables the circRNA to produce antigen in a sustained manner and possibly more powerful and prolonged immune responses [49]. This long-term presentation of circRNA vaccines can result in sustained humoral immunity, which is important in the prevention of chronic infections and re-infection [45,49].

Limitations and Challenges of mRNA Vaccine Technology

Although mRNA vaccines have proven to be quite successful, their broadly scaled application is subject to various inherent weaknesses such as their comparatively low translatability into a functional protein, as well as, the difficulties imposed on their effective delivery without off-target effects [58]. These

issues require further studies to improve the optimization of mRNA formulations, delivery, and production to ensure their therapeutic potential reaches its greatest potential and reduce adverse events. Besides, due to its inherent immunogenicity, unmodified mRNA may occasionally cause unwanted innate immune responses, which requires some chemical modifications to mitigate the effects, further complicating their development [49]. Moreover, due to the rapid breakdown of linear mRNA, the design and delivery systems must be developed with caution to maintain a desired level of stability and intracellular absorption, which represents another challenge on the way to sustained treatment efficacy [48,59].

On the other hand, the circular RNA structural integrity that is due to the covalently closed loop inherently provides enhanced resistance to exonuclease degradation, an essential way of solving the stability problems associated with the linear mRNA constructs [49]. Manufacturing and Distribution: The fact that large scale production and purification of mRNA vaccines are not only complicated, but expensive, poses an additional barrier to global availability, particularly in contrast to more established vaccine platforms. Storage and distribution requirements of cold chains only add to these difficulties, especially where there are limited resources in the context of the resource-constrained settings, where special infrastructure is typically absent. Cold Chain Requirements and VaccinationDue to the fragile nature of mRNA vaccines, cold chains require high standards, which creates significant logistical pressures and further complicates the situation in areas lacking proper infrastructure [19].

This is especially relevant to self-amplifying mRNA vaccines that, although they can be lower dose, better immunogenic, are larger and more challenging to produce, and purify, and prone to degradation [60]. Scalability of Production and Global AccessThe unpredictability of linear mRNA, along with the lack of specificity of the delivery systems based on lipid nanoparticles, further enhances these problems, requiring cold storage and causing a comparatively brief immune response [61]. On the contrary, the budding area of circular RNA [circRNA]-vaccines are more stable and have more longevity in antigen expression because of its distinctive loop shape, which could avoid the problem of degradation in regard to linear mRNA [62]. This improved stability may indicate a lower cold chain and increased global availability of circRNA-based vaccines [26,49]. The advances of artificial in vitro production of circRNAs also indicate its use in the next-generation RNA vaccines, yet its optimization, delivery, and use still need a lot of research and testing [48]. Additionally, safe ionizable lipids are developed to help with optimal mRNA encapsulation and delivery, which is essential in further developing the linear and circular RNA vaccine technologies [11]. The pace of clinical trials, setting up of a mass production facility and access to raw materials have continued to pose challenges to the mass-scale implementation of vaccines [63]. The major shortcoming of mRNA vaccines is their need to use proprietary ionizable lipids and stable supply of GMP raw materials to manufacture LNPs, as well as complex manufacturing methods [64].

Safety and Adverse Events

Ordinary Reactogenicity and Systemic Side EffectsThese are rather mild and temporary effects, which may include fever, fatigue, headache, and myalgia, and tend to manifest the strong immune response caused by the vaccine [65]. Nevertheless, continuous monitoring and investigation is essential to define and describe any uncommon or serious adverse events, such as the possibility of immune response or inflammation, especially in cases of repeated dosing or in high-risk groups [25,66]. Uncommon Adverse Events and Risk-reduction MeasuresAn example is that particular ionizable lipids in the composition of LNPs can be oxidized to generate aldehyde adducts thus promoting instability and the generation of unwanted byproducts [26]. Additionally, the synthetic miRNA mimics or antagomirs could cause activation of the immune system especially when the delivery system integrates some foreign bodies such as viral vectors or nanoparticles, which require careful safety considerations [25]. Circular RNAs [circRNAs] are intrinsically stable, so much of these issues may be alleviated by reducing the dependence on these potentially reactive elements; however, their immunogenicity and off-target effects are still subject to active research [48,49].

The exonuclease-resistant closed-loop structure of circRNAs that enables sustained levels of antigen expression is also a possible mediator of circRNA interactions with innate immunity systems,

potentially resulting in a more controlled or suppressed inflammatory reaction in contrast to linear mRNA [26,59]. This stability and exonuclease resistance also makes circRNAs a promising alternative, which may ease the requirement of stringent cold chain storage and ensure some of the issues of immunogenicity that are related to linear mRNA platforms [49,57,67]. Although circRNAs are more stable, residual double-stranded RNA in circRNA vaccines has the potential to stimulate innate immune reactions, which is excessively activated by myocarditis with mRNA vaccines, so that further studies on this matter are justified [68]. However, some circRNAs may alter the normal functioning of innate immunity by binding to pattern recognition receptors such as PKR, hence, regulate the levels of inflammation [57].

Table 3: Future Directions and Technological Advancements in mRNA Vaccines.

Innovation Area	Technological Approach	Mechanism	Expected Outcome	References
Thermostable mRNA vaccines	Advanced lipid nanoparticles and lyophilization	Enhanced mRNA stability at higher temperatures	Improved global distribution	[16, 26]
Self-amplifying mRNA [saRNA]	Incorporation of replicase genes	Intracellular amplification of antigen expression	Lower dose, prolonged immunity	[17, 27]
Multivalent and pan-viral vaccines	Encoding multiple conserved antigens	Broader and variant-resistant immunity	Reduced need for frequent boosters	[18, 28]
Mucosal mRNA vaccines	Intranasal and oral delivery systems	Induction of local mucosal immunity	Reduced viral transmission	[29, 30]
Personalized and therapeutic vaccines	Patient-specific antigen encoding	Targeted immune activation	Applications in cancer and chronic infections	[19, 31]
Rapid pandemic preparedness	Platform-based modular vaccine design	Faster antigen replacement and production	Accelerated outbreak response	[20, 32]

Viral Evolution and Antigenic Drift

Difficulties of the Rapidly Evolving VirusesThe rapid evolution of the viruses that is marked by the antigenic drift and shift often makes the existing vaccines less effective, thus requiring the ongoing reformulation and development of the new vaccine strategies. The challenge persists, highlighting the necessity of the platforms capable of adapting to new variants as fast as possible and, to this end, it may be the self-amplifying mRNA [saRNA] and circular RNA [circRNA] technologies that can have new development cycles in as little as several days, which is far quicker than traditional vaccine modalities [69]. Urgent Demand Tightly Clustered between Circular RNA Vaccines and Broad-Spectrum VaccinesThis need has led to the consideration of the circular RNA vaccines, which, with its natural stability and long-term expression, may offer a wider range of immunity and more durable immunity against emerging pathogens, and may result in a decreased rate of updating vaccines. In fact, the circRNA technology enables the rapid development of vaccines, whereby through the availability of viral sequences, or mutated sequences, there is a quick adaption to new viral strains [70].

Moreover, they have a long half-life, potentially up to 48 hours, which adds to the prolonged antigen presentation, which is an essential attribute of inducing effective and long immunity [57]. Moreover, circRNAs may potentially be longer-acting antigens with fewer immune-inducing effects, as circRNAs can avoid immune response activation, particularly when N6-methyladenosine is introduced, which makes them superior to conventional mRNA platforms [57]. Moreover, circRNAs appear to be more stable, which can also result in more consistent and sustained antigens presentation and, therefore, a more robust and durable adaptive immune response than linear mRNA vaccines [68]. These inherent difficulties in developing circular RNA [circRNA] vaccines are actively being overcome to achieve

maximum use of these benefits, including low immunogenicity but high antigenic yields and high circularization efficiency [49]. They are however, resistant to exonuclease degradation because of their closed-loop architecture enabling them to express their proteins stably and longer than the linear mRNA vaccines [71]. It is this structural integrity that makes circRNAs an arguably better platform on which a vaccine can be developed, especially when a situation arises, and a strong immune response needs to be developed and sustained through long-term expression of antigens [70].

An example is circular RNA vaccines with the receptor-binding domain of SARS-CoV-2 variants, which have shown protection efficacy against different strains such as Delta and Omicron in animal models [72]. It was reported that circular RNA vaccines have the ability to elicit a strong neutralizing antibodies and T-cell responses and result in full viral clearance in animals [26]. Such persistent expression and robust activation of immunity indicates that circRNA vaccines may provide partial immunity against viral infections, even against those of the fast-evolving ones [53,68]. In addition, intrinsic immunogenicity of certain circRNAs, especially with certain secondary structures or sequence motifs, can also be used as an adjuvant and provide an additional boost to the effect of vaccines by activating innate immune pathways [48,55]. This innate immune signaling capability, which is a property of circRNAs, sets them apart amongst many traditional vaccine platforms and creates opportunities to create self-adjuvated vaccines [48,56]. Such inherent immunostimulatory response, coupled with their tremendous stability and extended translational functionality makes circRNAs revolutionary in cancer immunotherapy [73].

Future Prospects and Innovations in mRNA Vaccines

Although linear mRNA vaccines have shown much success, the new technology of circular RNA [circRNA] vaccines is a breakthrough in this area as it has the advantage of being more stable and long-lasting of expression, which is attributed to its closed-loop and covalent form [34,68]. This structural property enables circRNAs to be resistant to exonuclease degradation, eliminate the requirement of nuclear translocation, and circumvent certain limitations of traditional mRNA platforms [48,74]. In addition to the stability, circRNAs have additional potential to serve as microRNA sponges or to interact with RNA-binding proteins, which broadens their therapeutic application [75]. Certain circRNAs, in particular, those that possess specific structural features, are translatable, and thus could be utilized as a new vaccine [76]. Indicatively, a COVID-19 circRNA vaccine was shown to be continuously expressed in cells over a period of six days, in contrast to the two-days of expression of a self-designed mRNA vaccine [68]. This long-term stability is equal to long-term antigen presentation, as it is an essential factor in inducing long-term and strong immune responses [55]. The implications of this sustained expression profile on vaccine efficacy are enormous, potentially enabling reduced dosage and fewer doses with the body still having strong immunogenicity [77]. Moreover, the distinct genesis of circRNAs due to nonsequential back-splicing of pre-mRNAs provide them with excellent stability than linear mRNAs making them excellent vaccine candidates that need long-lasting antigen expression [78].

Next-Generation mRNA Vaccine Platforms

Self-Amplifying mRNA [saRNA] Self-amplifying mRNAs [saRNAs] have the advantage of self-replicating once within the host cells, with the result of sustained and high-level expression of antigens using a smaller initial dose as compared to traditional mRNA vaccines. Circular mRNA and Other New ConstructsThese are engineered circular RNA-based constructs that are superior to nucleases and long-lasting antigen expression, which should be considered as the next generation of vaccine platforms [48,49]. Moreover, circRNA vaccines have shown the ability to induce a strong B-cell and T-cell immune response to pathogens, such as SARS-CoV-2, in preclinical models [74].

This strong immunological character highlights their possibility of coming up with highly effective prophylactic and therapeutic vaccines [79]. Their circular structure also enhances their stability to be degraded by exonucleases over a longer time than the linear mRNA and is also attributed to the sustained antigen presentation and sustaining immunities [78]. The possibility of circRNAs functioning as miRNA sponges also underscores the diverse functions of the miRNAs, which may explain their impact on viral pathogenesis that could alter host miRNA functions [80]. In addition to direct action as vaccine antigens, circular RNAs are microRNA sponges, protein modulators, and protein activity regulators, and their biological functions in eukaryotic cells are diverse [19,75]. This natural flexibility,

along with their unprecedented stability, makes circRNAs excellent candidates to diagnostic and therapeutic use true to viral infections and beyond [48,81]. The exogenous circRNAs and their capacity to induce immune reactions and prevent viral infections once again highlight their usefulness as therapeutic agents and vaccines [56]. The more stable and safer alternative of mRNA vaccines are engineered circular RNAs, which combine open reading frames and internal ribosome entry sites and with which it is easier to manufacture [77].

Advanced Delivery Systems

Alternative Nanoparticle FormulationsIn addition to the structural benefits of circRNAs, these new delivery methods play a crucial role in maximizing the intracellular delivery, the preventing the degradation of the RNA, and the production of antigenic proteins [77]. Uninjectable Routes of Administration. These are alternative delivery methods that were developed to increase patient compliance and expand the access and reach of vaccines by not necessarily requiring an injection with the use of a needle. Such high-level delivery systems, such as lipid nanoparticles, are necessary to overcome biological obstacles and improve the therapeutic index of mRNA and circRNA therapeutics based on achieving targeted and efficient uptake of cells [11]. The invention of new circular RNA [circRNA] vaccines has also been very promising, and some of them are already in clinical trial, which proves that they can be the next generation of antiviral drugs [13]. Furthermore, studies suggest that optimization of exon length and wise choice of efficient structural elements of internal ribosome entry site are essential to improve the efficiency of protein translation by circRNA vaccines [68].

Moreover, the investigation of approaches toward enhancing the immunogenicity of circRNA vaccine platforms including co-delivery with adjuvants or inclusion of immunostimulatory motifs is a significant research avenue in the future. These developments are essential considering the increasing anxiety about global pandemics and the enduring risk of new infectious illnesses, which demands the creation of highly flexible and generally protective vaccine platforms [49]. CircRNAs also possess unique properties such as high resistance to degradation and reduced immunogenicity, which places them as promising diagnostic/ prognostic biomarkers of viral infection [82]. Besides, virus-encoded circRNAs, or VcircRNAs, are now more known to regulate viral infection, immune modulation, and antiviral defense, and this creates new possibilities of therapeutic intervention and vaccine production [48,83].

Broadening Applications

Universal Vaccines [e.g., Pan-Influenza, Pan-Coronavirus] universal vaccines are developed to target a wide range of strains and future forms of pathogens, which limit the frequent update of vaccines and improves the preparation of the pandemic. Therapeutic Vaccines [e.g., HIV, Cancer] Therapeutic vaccines, including circRNA-based ones, are a major shift in paradigm in that they aim to treat existing diseases, including chronic viral infections and cancers, by regulating immune responses [81]. This new therapy is based on mobilizing the immune system to identify and destroy diseased cells and thus represent a highly specific and potentially curative way of treatment of diseases that seemed previously untreatable. This also implies that non-coding RNAs [ncRNAs], including circRNAs, have potential to be immune modulators and micropeptide encoders that is essential towards understanding viral infection and evasion mechanisms and eventually enabling better control of herpesviral infections and oncogenesis [57]. Moreover, the awareness that some non-coding RNAs, including the long non-coding RNAs, are capable of synthesizing micropeptides that are further displayed by MHC molecules, implies that these molecules have a more extended role in triggering the adaptive immune responses [57].

This changing concept of non-coding RNAs supports their versatile application in pathogen immunology and therapy [especially when noted in viral infection and anti-viral therapy] [48]. As a result, scientists are exploring the possibilities of circRNAs as biomarkers of viral infections, as well as a part of antiviral vaccines [48]. Further insight into the mechanisms of circRNA development and role during viral infection is essential to utilize their therapeutic values [84]. An example is the potential of circRNAs to control the viral replication and immune responses of hosts, which place them in the midst of the sophisticated virus-host response [70].

Role in Pandemic Preparedness

Rapid Response CapabilitiesThe quickness to design and implement vaccines in case of an outbreak is crucial, and this requirement implies both agile platforms and scalability. Development of Emerging and Neglected Tropical DiseasesRecent advances in COVID-19 pandemic gave a fresh impetus to the development and application of RNA-based vaccine technology, such as circRNA, which proved to be incredibly effective and responsive to the global health crisis [49]. This fast-track innovation highlights how circRNAs will be of vital importance in upcoming pandemic preparedness plans and will provide a solid and adaptable basis to develop a vaccine against novel and re-emerging pathogens. The given rapid progress emphasizes the transformational potential of circRNA vaccines to fight future pandemics as well as to cure the broad spectrum of infectious diseases in a rapid and unprecedented manner [49]. CircRNA also offers attractive precursors to develop a vaccine against a larger range of pathogens, including those that cause neglected tropical diseases, which have not been approached to make a vaccine successfully [82]. Outside of vaccine development, the natural stability and immunomodulatory nature of circRNAs places them at the core of defining basic interactions between the virus and the host and finding new antiviral approaches [56,84,85]. In particular, circRNAs have been demonstrated to directly suppress viral replication and adjust host innate immune response, including interferon-b activation through interactions with viral proteins and cellular parts [48]. As an example, artificial circRNAs have been demonstrated to prevent production of proteins of hepatitis C virus by adsorbing cell miR-122, and purified circRNAs are able to induce immune responses mediated by RIG-I, which protect against viral infection [56,86].

In addition, viral infections have been known to dysregulate circRNA expression, which has been crucial in determining viral replication and pathogenesis [82,86]. This disregulation can be achieved in different ways, including circRNAs as microRNA sponges to regulate the expression of target genes, thus affecting the process of inflammatory regulation and innate immune reactions [87]. The complexity of the interaction between viral infection and circRNA expression improves the platform upon which innovative antiviral therapy and diagnostics can be developed [86,88]. The study of the interaction between circRNA and the host immune system during antiviral defense will be further understood with further research into the spatiotemporal regulation of circRNA function, such as alterations in localization patterns, over time [78]. The pharmacological or genetic regulation of circRNA expression or stability might thus be used to improve antiviral ability in cells [48]. This interaction implies that alterations in circRNA biogenesis or activity may be the root of autoimmune diseases, and it can be even further investigated how they influence the immune regulation [89].

Beyond vaccine development, natural stability and immunomodulatory properties of circRNAs put them in the center of the determination of fundamental interactions between the virus and the host and the identification of new antiviral strategies [56, 84, 85]. Specifically, circRNAs have been found to directly repress viral infection and host innate immune response, such as interferon-b-activation by viral protein and cellular components interactions [48]. Using the example of artificial circRNAs, which can prevent hepatitis C virus protein production by adsorbing cell miR-122, purified circRNAs can induce immune responses by the RIG-I anti-viral response [56,86]. Moreover, viral infections are also known to disrupt circRNA expression and this has played an essential role in the viral replication and pathogenesis [82,86]. Such disregulation is possible in various forms, such as circRNAs as microRNA sponges to control the expression of target genes and hence influence the mechanism of inflammatory control and innate immune responses [87]. The interplay between viral infection and circRNA expression is complicated, which enhances the platform on which innovative antiviral therapy and diagnostics can be made [86,88]. The interaction between circRNA and host immune system during antiviral defense is going to be studied further with more detailed research on the spatiotemporal regulation of circRNA activity, including changes in localization patterns across time [78]. Antiviral capacity in cells could therefore be enhanced through the pharmacological or genetic control of circRNA expression or stability [48]. It means that the cause of autoimmune diseases can be changes in the circRNA biogenesis or activity, and it can even be more thoroughly explored how they can affect the immune regulation [89].

Conclusion

mRNA vaccines have revolutionized the field of vaccinology by offering a rapid, adaptable, and highly effective approach to preventing viral infections. Their ability to induce strong immune responses and be developed quickly has proven invaluable during global health emergencies, particularly the COVID-19 pandemic. Despite their demonstrated efficacy, several limitations including cold-storage requirements, unequal global distribution, durability of protection, and public acceptance—continue to challenge their widespread implementation. Advances in mRNA stabilization, delivery technologies, and next-generation formulations are actively addressing these concerns and broadening the scope of mRNA vaccines to other viral diseases. As research progresses, mRNA vaccines hold significant promise not only for infectious disease control but also for future applications in personalized medicine and pandemic preparedness. Strategic investment, global collaboration, and continued surveillance will be essential to maximize their long-term impact on public health.

Ethical Approval

Not Applicable

Conflict of Interest

The authors declare they don't have any conflict of interest.

Author contributions

The original author and the supervisor of the cross-ponding author write the work's initial drafts. Each author contributed to the article, gathered information, edited it, made tables, and received approval to submit it to a journal for publication.

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