International Journal of Health Sciences and Research
Vol.12; Issue: 7; July 2022
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

mRNA Vaccine - Game Changer against Infectious Disease

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DOI: https://doi.org/10.52403/ijhsr.20220737

ABSTRACT

Millions of diseases are prevented each year by vaccines, saving thousands of lives. A variety of paediatric diseases have been significantly reduced over the past decade as a result of widespread vaccinations, including smallpox, measles, and polio. The ability of mRNA vaccines to evolve rapidly, their high potency, and the potential for low-cost and safe delivery, make them a promising alternative to traditional vaccines. However, until recently, their use was limited because to the instability and inefficiency of mRNA distribution in vivo. Non-infectious disorders, such as cancer, may not be amenable to traditional vaccine techniques. Due to this, there is a great need for more powerful and diverse vaccination platforms. This Review examines potential directions and problems in bringing this promising vaccination platform to mainstream therapeutic usage.

Keywords: mRNA Vaccine, Infectious Disease, COVID-19 mRNA vaccines, vaccination drive

INTRODUCTION

Vaccines have been proven to be the most effective method of preventing and controlling disease in medical history. [1]. Many lives and large amount of money have been saved through the successful development and use of vaccines. [2]. The potential uses of vaccines include not only preventive and therapeutic treatment for infectious diseases, but for cancer, as well as a means for eliminating allergens [3]. Although this achievement has been made, many challenges still remain in developing vaccines, especially for diseases that are better able to resist the adaptive immune response [4]. Additionally, the key limiting factor for most viral vaccines is not the efficiency of conventional techniques, but the need for rapid research and development and large-scale deployment. As a final point, traditional vaccination methods may be ineffective against non-infectious disorders like cancer. Consequently, more adaptable and effective vaccination platforms are urgently required There are possibilities to replace traditional vaccinations with nucleic acid therapies. Reporting gene mRNA injections into mice to induce protein synthesis led to the first study using in vitro transcribed (IVT) mRNA in animals in 1990 [5].

Furthermore, a 1992 study found that injecting vasopressin-encoding mRNA into the hypothalamus could elicit physiological responses in rats. [6]. Due to concerns about mRNA instability, high inherent immunogenicity, and poor in vivo delivery, there have been few investments in the development of mRNA therapies despite their early promising results. Rather, DNA- and protein-based therapeutics have been explored [7, 8]. As a result of significant technological advancement and research expenditure over the last decade, mRNA has

emerged as an effective therapeutic tool in the fields of vaccine development and protein replacement therapy. There are several benefits to just using mRNA over subunit, killed, and recombinant viral vaccines, and also DNA-based vaccines. To begin with, there is also no risk of infection or insertional mutagenesis even though mRNA is a noninfectious, non-integrating platform. Furthermore, even though mRNA is broken naturally, its half-life in vivo could be influenced through suitable modification and delivery methods [9-12]. The intrinsic immunogenicity of mRNA can be reduced to improve the safety profile. Second, in terms of efficacy, certain modifications make mRNA more stable and translatable. [9, 12, 13]. It is possible to achieve effective in-vivo administration by converting mRNA into carrier molecules that allow for rapid cytoplasmic absorption and expression. [10, 11]. Due to the fact that mRNA is the smallest genetic vector, anti-vector immunity is prevented, Third, because of the high yields of in vitro transcription mechanisms, mRNA vaccines hold the promise of quick, low-cost, and scalable production. In terms of manufacturing and application, mRNA has a high degree of flexibility as the technological foundation of medicines and vaccines. Because any protein can be encoded and produced by mRNA, it is theoretically possible to develop vaccines and protein replacement therapies for diseases as diverse as infections and cancer. Because the encoded protein only alters the sequence of the RNA molecule rather than its physicochemical properties, diverse vaccines can be produced using the same established manufacturing process without requiring any adjustments, saving time and money. In terms of efficacy, mRNA-based treatments benefit from the fact that, unlike DNA, they do not need to cross the nuclear membrane. Unlike peptides, there is no MHC haplotype restriction for mRNA vaccinations. Furthermore, mRNA attaches to pattern recognition receptors, and mRNA vaccines may be engineered to be self-adjuvanting, which peptide and protein-based vaccinations do not [14].

The field of mRNA vaccines is rapidly evolving, and over the past several years' considerable preclinical evidence has emerged, along with a number of human clinical trials. The Review examines existing mRNA vaccination techniques, presents the most recent information, discusses recent triumphs and problems, and offers suggestions on what might come next According to the findings, mRNA vaccines have the potential to solve several of the problems that have plagued vaccine development for highly contagious diseases like cancer.

History and development of mRNA vaccine:

The recently developed COVID-19 mRNA vaccines are the first of their kind, but they didn't come about overnight. The discovery of RNA took place in the 1960s. Then, in the 1970s, basic research laid the basis for the development of vaccine in the 1990s, optimization in the 2000s, influenza and rabies clinical trials in the late 2010s, and the creation of SARS-CoV-2 vaccines in early 2020. The journey of mRNA vaccine development is detailed in **Figure 1**.

In 1989, researchers disclosed the first successful transfection of customized mRNA encapsulated within a liposomal nanoparticle into a cell [15, 16]. A year later, "naked" (or unprotected) lab-made mRNA was delivered into the muscle of mice [17,18]. These researches provided the first proof that in vitro produced mRNA from a specific gene may convey the genetic information needed to make a particular protein within living cell tissue [17], leading to the notion of messenger RNA vaccines [19,16,20]. In 1993, it was discovered that liposome-encapsulated mRNA expressing a viral antigen stimulated T lymphocytes in mice [21]. The next year, self-amplifying mRNA was created by combining a viral antigen with a replicase producing gene [21, 22]. In mice, the approach was utilized to stimulate both a humoral and cellular immune response against a pathogen

[21]. The next year, it was shown that mRNA encoding a tumour antigen elicited a comparable immune response against cancer cells in mice [23, 24].

Woff et al. revealed mRNA vaccines were successful for direct gene transfer [25]. Currently, commercially available mRNA vaccinations fall into two categories: conventional mRNA vaccines and self-amplifying mRNA vaccines derived from positive strand RNA viruses. Despite being tried in the early 1990s, mRNA vaccines were not widely used because of concerns about their fragile stabilization caused by ubiquitous ribonucleases and their small scale of production. A 1995 study by Ross and colleagues proved that mRNA stability may be increased by enhancing formulation and optimization [26].

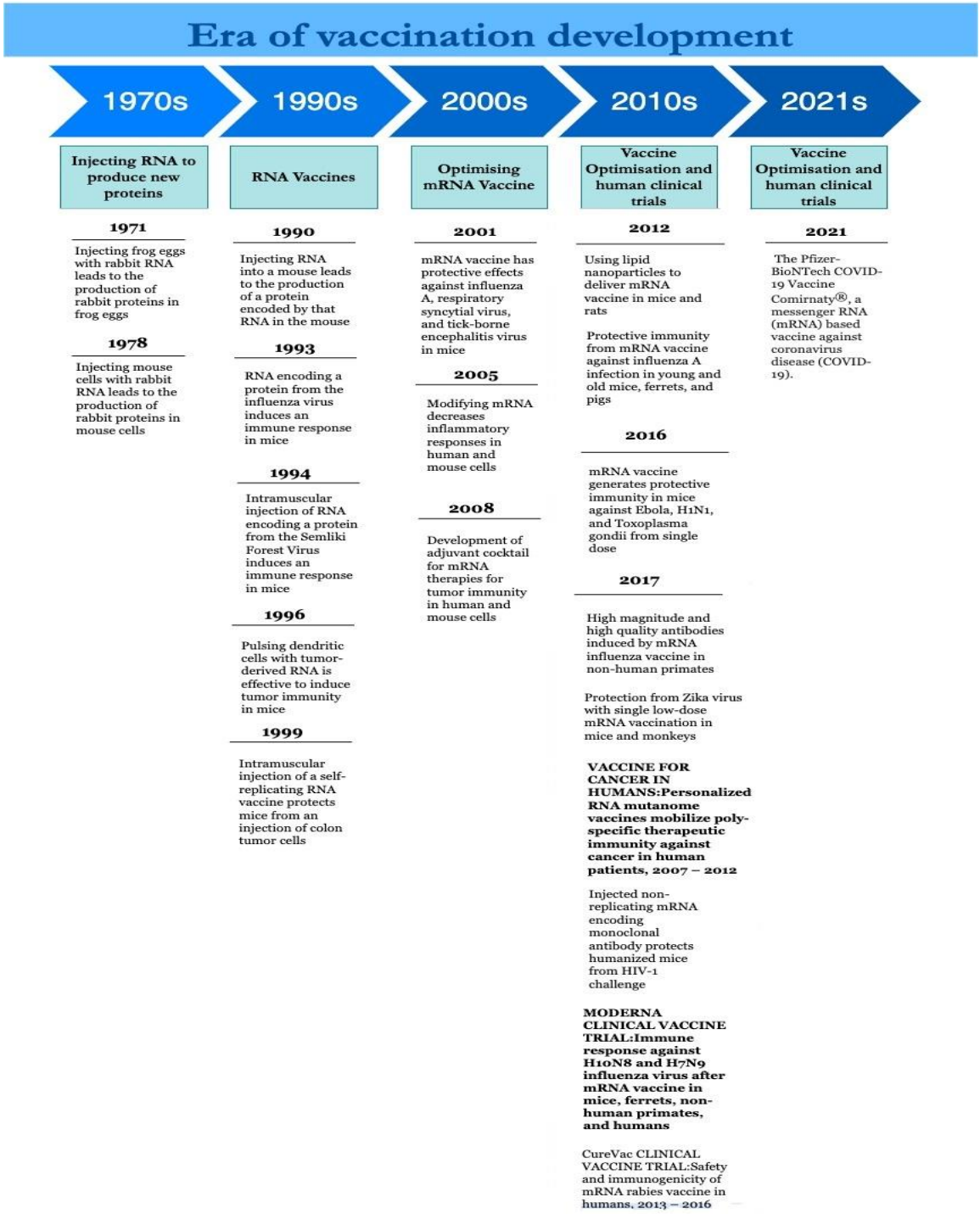

Figure 1: Journey of mRNA Vaccine Development

Researchers have since continued to study mRNA vaccines, and mRNA can now be synthesized synthetically by enzymatic transcription process performed in a cell-free environment. A linearized plasmid DNA template, recombinant RNA polymerase, and nucleoside triphosphates are used to produce the vaccine, along with a linearized plasmid DNA template and the mRNA vaccine, respectively. In a one-step process, a cap structure is synthesized from an enzymatically attached cap structure or as a transcriptional product Finally, a poly(A) tail will be added to complete the mRNA sequence. In their most basic form, conventional mRNA vaccines have an ORF for the target antigen is flanked by untranslated regions (UTRs) and a poly(A) tail in conventional mRNA vaccines. Transfection with them promotes transient antigen expression. Apart from traditional vaccines, the development of these mRNA vaccines uses a viral engineered genome containing genes that encode RNA replication machinery. In addition, the structural protein sequences are replaced with the gene of interest (GoI), and resulting genomes are called replicons. Known as self-amplifying mRNA, these vaccines are capable of self-replication by generating duplicate copies of the antigen-coding mRNA and expressing high levels of the heterologous gene when introduced into the cytoplasm of host cells, mimicking antigen production by viral pathogens in vivo, and triggering both humoral and cellular responses [27-32].

In addition to Sindbis virus, Semliki Forest virus, and Kunjin virus, engineered genomes can be used to create self-amplifying mRNA, among other viruses [33-35]. RNA molecules can be synthesized on a large scale in vitro from DNA templates that form self-amplifying mRNAs (9-11kb) similar to ordinary mRNAs, and mRNAs can be self-amplifying from a DNA template. The RNA-dependent RNA polymerase that encodes the pure RNA replicon is widely translated and expanded after it is transported into host cells, either as viral particles or as synthetically formed RNA Published studies suggest that immunization with self-amplifying mRNA vaccines results in higher antigen expression levels that last for many days in vivo, compared to the quick production of traditional mRNAs. Equivalent protection is available, though at a higher price [36]. Because it lacks viral structural proteins, the replicon does not produce infectious viral particles. Furthermore, neither conventional mRNA nor self-amplifying mRNA may theoretically integrate into the host genome and will be destroyed spontaneously throughout the antigen expression process. These features suggest that mRNA vaccines have the potential to be far safer than conventional vaccinations and are a viable vaccine platform.

Principles of design and synthesis:

mRNA Synthesis and Modification in Vitro to date, mRNA in vitro transcription technology is mature, with the most common approach utilizing T3, T7, or SP6 RNA polymerase and linear DNA (linearized plasmid DNA or synthetic DNA synthesized by PCR) for mRNA synthesis. Five-prime cap (5’ cap), five-prime untranslated region (5’ UTR), open reading frame (ORF) region, three-prime untranslated region (3’ UTR), and poly (A) tail structure are some essential structural features of mature mRNA in the eukaryocyte that are necessary to maintain mRNA functional [37,38]. It is advantageous for mRNA stability and expression capabilities to maintain structure. The effectiveness of an mRNA vaccination can be increased even more by altering the mRNA sequence in accordance with its complete structure. On the other hand, a mixture of specific target mRNA, transcriptomic RNA, nucleotides, oligo deoxy nucleotides, and proteins make up the first product of mRNA in vitro transcription [39]. This method uses chromatographic techniques to separate the target mRNA from other mRNA impurities while precipitation and extraction procedures are used to remove common mRNA impurities. [40]. The design and synthesis mRNA are detailed in **Figure 2.**

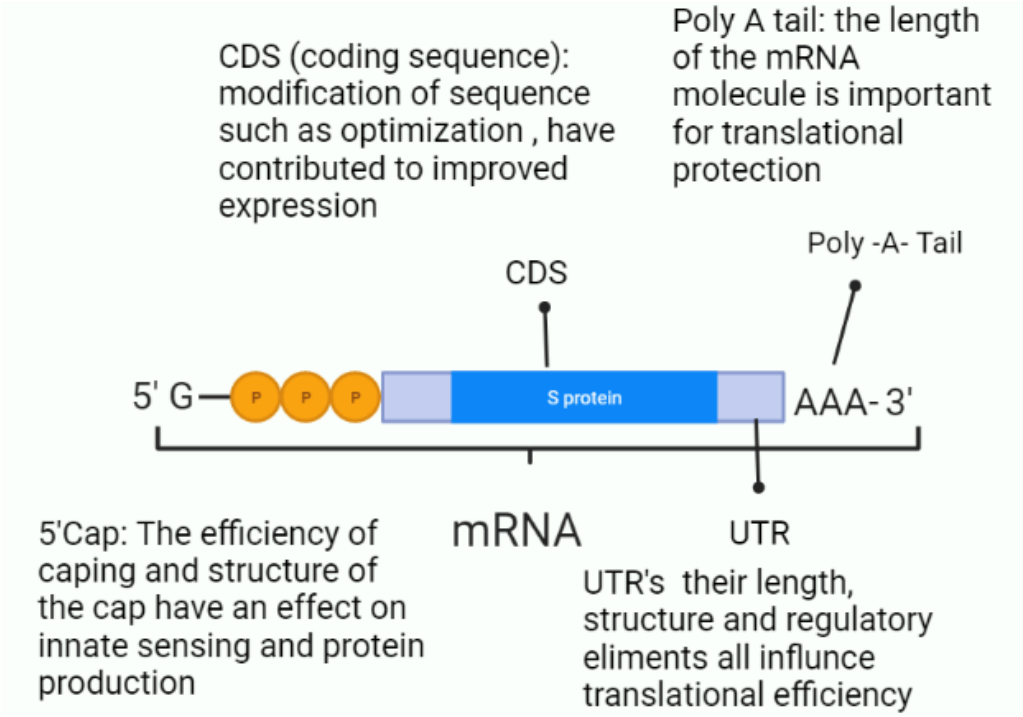

Figure 2: Design and synthesis of mRNA

Five-Prime Cap (5' cap) and Modification:

During mRNA in vitro transcription, mRNAs from eukaryotic and partly viral genomes have a 7-methylguanosine (m7G) cap at the 5' end of the mRNA sequence (m7GpppN structure), which forms a 50, 50-triphosphate bridge with the first RNA nucleotide (ppp). The 5' cap can remove free phosphate groups from the mRNA sequence by attaching to the eukaryotic translation initiation factor 4E. This significantly increases mRNA stability, enables the ribosome to recognise the start of the mRNA, and boosts translation efficiency (eIF4E) [41,42]. As a result, it is clear that 5' cap alteration can be critical to improving mRNA properties. In vitro mRNA capping, there are two techniques that are commonly used [39,41] To begin, adding a normal cap analogue, the m7GpppG structure, to the mRNA transcription system allows for mRNA capping as well as in vitro transcription. Second, following the first in vitro transcription, mRNA capping can be completed by a capping enzyme process [41, 43]. The most frequent capping technique for mRNA in vitro transcription is cap analogue, yet studies have reported that conventional cap analogue can reversely attach to the mRNA sequence [44]. In this instance, mRNA isomers develop, resulting in reduced mRNA downstream translation efficiency. Anti-reverse cap analogues (ARCA) have developed to prevent reverse incorporation of 5' cap [44, 45].

To guarantee that the methyl groups react with the hydroxyl groups at the right place during transcription, ARCA is changed at the C2 or C3 position. ARCA-capped mRNA has a better translation efficiency than normal cap homologue [44-46]. Further modifications to the ARCA structure have been made in recent years to increase mRNA characteristics. Phosphorothioate modification based on ARCA, for example, would boost mRNA translation efficiency by increasing its affinity for eIF4E, as well as its sensitivity to decapping enzymes, so improving mRNA stability [47-49]. In immature dendritic cells (DCs), Kuhn et al. showed that m27,2'OGppSpG (-S-ARCA) may increase mRNA stabilisation and translation efficiency [47]. In 2016, Strenkowska et al. created "2S analogues," which were cap analogues modified with 1,2-dithiodiphosphate, ARCA, and an elongated polyphosphate chain. Thanks to these

advantages, 2S analogues performed better than any S-ARCA used in clinical studies. [50]. In 2018, another cap analogue, "CleanCap," a co-transcriptional capping technique, was created [51]. It used an initial capped trimer to produce a naturally occurring 5' cap structure, increasing capping efficiency to almost 90–99 percent [52, 51].

Untranslated region (UTR) optimization:

UTRs are non-coding mRNA sequence segments found in the coding region's upstream (5' UTR) and downstream (3' UTR) domains. As was already mentioned, UTRs are involved in mRNA replication and translation processes. Through interactions with RNA binding proteins, they have the power to significantly alter mRNA degradation and translation efficiency [37,52]. It is critical to optimize UTRs while attempting to improve mRNA stability and translation efficiency. In general, UTR optimization aims to boost mRNA expression in vivo [42]. The commonly utilized 3' UTR sequence generated from α-globin and β-globin, for example, has translation and stability regulatory components. Because 3' UTR is thought to be a concentrated area of unstable components in mRNA, avoiding unstable sequences while generating 3' UTR can boost mRNA stability. This is illustrated by AU-enriched sequences and GU-enriched sequences [53, 54]. Introducing stable components to the 3' UTR, on the other hand, can greatly increase mRNA stability and extend its half-life. Orlandini von Niessen et al. successfully increased mRNA translation efficiency by connecting two random 3' UTRs that included stable components in succession [55, 56]. Because the 5' UTR has a direct effect on the translation of its downstream sequence ORF, the optimization of the 5' UTR should have no effect on the ORF's regular translation process. Avoiding the gene sequence in the 5' UTR, which is similar to the region upstream of the ORF, can successfully prevent false start and reading frame substitution during mRNA translation [57]. Additionally, certain sequences can be introduced to the 5' UTR to improve mRNA stability and translation accuracy. Kozak et al., for example, added the sequence GCC-(A/G)-CCAUGG in this region, resulting in a more accurate start of the translation process [58]. The study also found that an over-stabilized secondary structure of the 5' UTR hinders ribosome binding to mRNA, whereas a short and flexible 5' UTR is more favorable to ribosome binding [59].

ORF's (Open Reading Frame) codon optimization:

Since the ORF region codes for mRNA, its rate of translation is crucial. Therefore, choosing the best codons in this region can enhance mRNA translation efficiency as a whole. For highly expressed genes to be translated using the same host codons and/or to ensure tRNA abundance during the production of exogenous mRNA, optimised ORF sequences frequently include synonymous frequent codons and/or codons with greater tRNA abundance to replace rare codons in ORF [60]. However, a high mRNA translation rate is not always advantageous because some proteins require a low translation rate to fold properly, stably, and efficiently; in this situation, employing codons with low frequency in ORF can give higher-quality protein products [52]. As a result, various codon optimization algorithms should be used for distinct antigens to optimize mRNA translation rate while still ensuring expressed antigen quality.

Stability of the poly (A) tail and mRNA:

During mRNA translation, the poly (A) tail and the 5' Cap structures are both crucial. Poly (A) sequences can prolong in vivo half-life, increase stability, and enhance mRNA translation efficiency while slowing down RNA exonuclease degradation [52]. Additionally, the Poly (A) binding protein (PABP) can attach to the 5' Cap via eIF4G and eIF4E, altering the closed-loop structure of the mRNA and negatively affecting both

its stability and translation efficiency. [52, 61, 62]. PABP, on the other hand, can bind to adenylation complexes and assist in the translation suppression process mediated by microRNA. PABP's paradoxical function suggests that differing Poly (A) sequence lengths can alter mRNA translation efficiency differently.

There are several techniques for synthesizing a Poly (A) structure, one of which is in vitro transcription with a DNA template containing Poly (A) structural information, which can result in a specific Poly (A) sequence length [41]. After initial mRNA transcription, recombinant Poly (A) polymerase can be used to add Poly (A) structures by undergoing enzymatic polyadenylation, producing Poly (A) structural mixes with different lengths [41]. Preliminary studies suggest that a long Poly (A) sequence can enhance mRNA stability. For instance, the ideal Poly (A) sequence length for DCs is between 120 and 150 nucleotides [41, 63], whereas human primary T cells can benefit from Poly (A) sequence lengths over 300 nucleotides for improving mRNA stability and translation efficiency. [64]. When the length of the Poly (A) sequence is fewer than 20 nucleotides, the mRNA translation efficiency is reduced [65]. When the length of the Poly (A) sequence is fewer than 20 nucleotides, the effectiveness of mRNA translation is reduced. By utilising cutting-edge genome-wide research tools, Lima et al. found in 2017 that mRNAs with high translation efficiency have short Poly (A) sequences, in contrast to the frequent identification of short Poly (A) structures in well-translated eukaryotic mRNAs [62]. Therefore, adjustments should be made to maximise mRNA translation efficiency because the lengths of Poly (A) sequences required for high translation efficiency mRNA in various types of cells vary.

Delivery vehicles:

In order to achieve therapeutic relevance, in vivo mRNA distribution must be efficient. Exogenous mRNA must cross the lipid membrane barrier to enter the cytoplasm where it may be translated into functional protein. The processes of mRNA absorption appear to be cell type specific, and the physicochemical features of mRNA complexes can have a significant impact on cellular transport and organ distribution. Too far, there have been two fundamental techniques documented for the administration of mRNA vaccines [66]. The first step is to administer mRNA, with or without a carrier, directly into the intravenous fluid circulation. The second step involves administering mRNA, either with or without a carrier, directly into the intravenous fluid circulation. The cellular target, transfection effectiveness, and other cellular parameters can all be precisely controlled with ex vivo DC loading, a type of cell loading. It is a pricey and time-consuming vaccination technique. Even though accurate and effective cell-type specific delivery is still not possible with direct mRNA injection, it is quick and inexpensive, and there has been a lot of progress in this area. Numerous approaches have been used to investigate both of these concepts [67].

DCs are the immune system's most powerful antigen-presenting cells. Although DCs have been demonstrated to internalize naked mRNA via a number of endocytic mechanisms [69-71], Electroporation is commonly used to enhance ex vivo transfection efficiency; in this case, mRNA molecules are transported through membrane holes created by a high-voltage pulse and enter the cytoplasm directly [72]. This method of mRNA administration has become popular because to its capacity to achieve high transfection efficiency without the need of a carrier molecule. Ex vivo-loaded DCs are subsequently re-infused into the autologous vaccination recipient to kickstart the immune response. Because most ex vivo loaded DC vaccines elicit largely a cell-mediated immune response, they have mostly been employed to treat cancer [66]. Naked mRNA has been effectively employed for in vivo vaccinations, particularly in forms that preferentially target antigen presenting

cells, such as intradermal [69,73] and intranodal injections. Notably, a recent study found that repeated intranodal vaccinations with naked, unmodified mRNA encoding tumor-associated antigens elicited strong T cell responses and enhanced progression-free survival [74-76].

demonstrated an effective RNA delivery and immunization strategy in mouse models [78-81], but there is no evidence of efficacy in large animals or humans. In vivo electroporation has also been used to promote therapeutic RNA absorption [82-84]. Increased cell death and limited access to target cells or tissues can make physical approaches difficult. However, the field recently favoured [82].

Protamine, a cationic peptide, has been found to shield mRNA against destruction by serum RNases [85]; however, protamine-complexed mRNA alone showed poor protein production and effectiveness in a cancer vaccination model, presumably due to an extremely tight interaction between protamine and mRNA [14, 86]. This problem was overcome by creating the RNActive vaccination platform, which uses protamine-formulated RNA as an immune activator rather than an expression vector [87]. Many primary cells and cancer cell lines respond well to commercially available cationic lipid or polymer-based mRNA transfection reagents like TransIT-mRNA (Mirus Bio LLC) or Lipofectamine (Invitrogen) [9,13], However, they frequently show poor in vivo efficacy or a high level of toxicity. Many advances in the development of similarly designed complexing reagents for safe and successful in vivo application have been made, as detailed in numerous recent reviews. [10, 11, 88, 89].

Lipid nanoparticles (LNP) frequently include cholesterol, a stabilising agent, lipid-linked polyethylene glycol (PEG), which extends formulation half-life, and naturally occurring proteins and lipids, which support lipid bilayer structure. Ionizable cationic lipids also encourage self-assembly into virus-sized (100nm) particles and enable endosomal release of mRNA to the cytoplasm. [90]. Numerous studies have demonstrated that LNPs are effective for in vivo siRNA administration, but it was only recently demonstrated that LNPs are also effective for in vivo delivery of self-amplifying RNA and conventional [91], non-replicating mRNA [92]. Because of apolipoprotein E binding and subsequent receptor-mediated hepatocyte uptake [93], Systemically administered mRNA-LNP complexes primarily target the liver, and administration via intradermal, intravenous, or transdermal routes has been demonstrated to prolong protein expression at the injection site [92, 94]. The mechanisms of mRNA exit into the cytoplasm are unknown for both naturally occurring exosomes and synthetic liposomes. [95].

These mRNA-LNP expression kinetics could be useful for inducing immune reactions. A recent study discovered that high antibody titers, as well as germinal centre (GC) B cell and T follicular helper (TFH) cell responses, were influenced by persistent antigen availability following vaccination [96]. This approach might have contributed to the potency of newly published nucleoside-modified mRNA–LNP vaccines administered via intramuscular and intradermal methods [94, 97]. In fact, it has been discovered that TFH cells are an essential subset of immune cells that vaccines need to activate in order to produce potent and durable neutralising antibody responses, particularly against viruses that are immune-evading to humoral defences [98]. The kinetics of the GC reaction and TFH cell differentiation are also poorly known, and advancement in these areas will surely benefit future vaccine formulation.

Infectious mRNA disease:

Smallpox virus eradication is a prime example of how vaccines against pathogenic organisms have continuously been a very effective method of preventing infectious diseases. Ineffective against a number of persistent or recurrent pathogenic diseases with lengthy disease durations, such as AIDS and tuberculosis, are conventional

vaccination methods like non-live freeze-dried vaccines and live attenuated vaccines (TB). Due to their relatively lengthy development times, conventional vaccines would be unable to control outbreaks of virulent viruses like the coronavirus, the Zika virus, and the ebolavirus in the Zaire [99].

Influenza:

The disease is caused by influenza viruses, which belong to the Orthomyxoviridae family [100]. They are single-stranded RNA viruses with a negative sense. The influenza virus is made up of RNA polymerase subunits, viral glycoproteins (HA, NA), nucleoprotein (NP), matrix protein (M1), membrane protein (M2), nonstructural protein (NS1), and nuclear export protein (NEP) [101]. Human influenza viruses A and B cause viral respiratory disease [102]. A severe influenza pandemic, similar to SARS-CoV-2, killed more than 40 million people worldwide in 1918 [103]. An effective influenza vaccination will always be required. In the clinic, three types of influenza vaccines are now used: inactivated, live attenuated, and recombinant HA. These vaccines target the HA protein, which is involved in viral entry into the host [104, 105]. However, the virus's rapid mutation causes antigenic drift, necessitating yearly changes to the influenza vaccine. As a result, when a new influenza strain emerges, alternate antigen targeting and rapid vaccine production are critical. Many mRNA vaccines have been developed for the influenza virus. The VAL-506440 vaccine is composed of lipid nanoparticles (LNP) containing modified mRNAs that encode the full length, membrane-bound version of the hemagglutinin (HA) glycoprotein from H10N8 or H7N9 influenza strains [106, 107].

Rabies:

The rabies virus causes a central nervous system illness. The virus infects humans through the bite of an infected animal (cat or dog) [108, 109]. Following infection, humans experience flu-like symptoms followed by severe neurotropic symptoms caused by progressive encephalomyelitis. Despite the fact that several vaccines against the rabies virus have been approved, rabies infection still has a high mortality rate [110]. As a result, newer and more effective vaccine candidates are needed. There are several mRNA-based rabies vaccines undergoing clinical trials right now. Both the free and complexed forms of the mRNA encoding the rabies virus glycoprotein (RABV-G) with the cationic protein protamine are present in the two lyophilized, temperature-stable mRNA candidate vaccines CV7201 and CV7202. Germany has approved CV7201 for use in Phase 1 clinical trials. New rabies vaccine CV7202 is presently undergoing phase 1 clinical trials. 53 people have been recruited so far for the investigation, which is scheduled to be finished in 2023 [111, 112].

Zika virus

The Zika virus is transferred to humans through the bite of an aedes mosquito, followed by direct transfer of the person who is infected with a person infected with saliva or sexual contact. Zika is a positive RNA virus with three structural proteins: capsid (C), pre-membrane (PRM) and envelope (e) and seven structural proteins (NS1, NS2a, NS2B, NS3, NS4A, NS4B, NS3, NS4A, in extreme situations, ZIKV infection causes a moderate influenza disease as well as a multi-governitis insufficiency, meningitis and encephalitis. Membrane and envelope protein (prME) is a popular antigen for Zika virus mRNA vaccines because neutralizing antibodies against prME can prevent virus fusion [113] mRNA-1893 is also another mRNA-based vaccine that targets the Zika virus's pre-membrane and envelope (prM-E) glycoproteins. PrM-E is the antigen of selection for Zika virus mRNA vaccines because neutralising antibodies against it prevent highly contagious fusion to the host cell. This vaccine is currently undergoing Phase I clinical trials to assess its safety, tolerability, and immunogenicity, with results expected by 2021. (NCT04917861). Another mRNA-based vaccine, mRNA1325,

completed phase I clinical trials in 2019, but the results have yet to be published (NCT03014089). Because there is currently no approved Zika virus vaccination, these mRNA-based vaccines may be useful in treating Zika virus infection [114].

HIV:

AIDS (acquired immunodeficiency syndrome) is caused by HIV, a Retroviridiae virus [115]. HIV is made up of a 5' long terminal repeat region (LTR) that codes for a promoter for viral gene transcription, the gag gene reading frame that codes for the outer core membrane (MA), capsid protein (CA), nucleocapsid (NC), and a nucleic acid stabilizing protein and a nucleic acid stable Protease (PR), reverse transcriptase (RT), RNase H, and integrase are all encoded by the pol gene, which comes after gag (IN). Two envelope glycoproteins, gp120 and gp 41, are encoded by the env gene, which is located next to the pol gene [116]. HIV became a pandemic, infecting 17.5 million people worldwide [117]. HIV is spread through direct human-to-human transmission [118]. Despite many years of research, there is currently no viable HIV vaccine. A self-amplifying mRNA vaccine expressing clade C envelope glycoprotein and a viral replicon particle (VRP) was tested in rhesus macaques. Anti-Env levels in animals given the HIV SAM and HIV-VRP vaccines ranged from 103 to 104.5, with GMTs of 103.94 and 103.41, respectively [117]. Following boosting with Env/MF59, anti-Env antibody titers increased significantly, reaching values 10–100-fold higher than those seen after priming with Env/MF59, HIV SAM, and HIV-VRP peak GMTs of 106.14, 106.25, and 104.79, respectively [118, 119]. Another preclinical study looked at the mRNA encoding the HIV gag gene, which produced antigen-specific, functional T cells, resulting in potent cytotoxic T lymphocytes. Mice were given an intravenous injection of an LNP-encapsulated, nucleoside-modified mRNA expressing VRC01 to see if they developed neutralizing antibodies. This single-dose method protected mice from HIV-1 intravenous challenge. As a result, mRNA vaccines have the potential to be effective vaccine candidates against HIV infection [120].

SARS Covid-19:

Over the past 20 years, there were three coronavirus infections (severe acute breathy syndrome coronavirus (SARSCoV), and SARSCoV2), all of the extreme health threats and enormous loss economically in the absence. Only three mRNA vaccine patents have been granted out of all vaccine-related patents as of today, the majority of which are linked to SARS and MERS. In the event of a sudden new coronavirus pandemic, the rate of vaccine development influences the speed with which lives can be saved [121]. As a result, mRNA vaccines with a rapid product process will undoubtedly play an essential role in the advancement of coronavirus vaccines. COVID-19, which is resulted by SARS-CoV-2 infection, had spread around the world as of August 25, 2020, with over 23.51 million cases reported and over 810,000 deaths. (Source: World Health Organization) The development of a vaccine that would be both safe and effective is critical. Lin et al. discovered two non-replicating mRNA vaccines that express the receptor-binding domain of the spike protein and the virus-like particles (VLPs) of Severe acute respiratory, respectively; additional antigen sequence optimization, as well as safety and efficacy studies, are currently under way [122]. Moderna announced mRNA-1273, a SARS-CoV-2 mRNA vaccine candidate, and formally launched Phase I clinical studies for safety and immunogenicity assessment on March 16, 2020. In this vaccine, the spike (S) protein of SARS-CoV-2 is encoded in a perfusion stabilized state. According to preliminary results released on May 18, 2020, mRNA-1273 was found to be generally safe and well tolerated; two weeks after the second dosage, with a vaccination dose as low as 25g, levels of both binding and neutralizing antibodies in serum were comparable to those found in samples from COVID-19 patients. The date

is March 27, 2020. Sanofi Pasteur and Translate Bio have announced a partnership to develop a novel SARS-CoV-2 mRNA vaccine. The current phase I/II clinical studies of BNT162b1 have yielded positive results, according to Pfizer and BioNTech. LNP created an mRNA vaccine candidate that contained a trimerized SARS-CoV-2 S protein receptor binding domain. BNT162b1 dosage levels were initially determined to be between 10 and 30 g. After two doses of 10g and 30g BNT162b1, including both, the mean titers of specific neutralising antibodies have been 1.8-fold and 2.8-fold higher than the convalescent's specific neutralising antibody [123].

mRNA Vaccine Immunity:

The immune response to the mRNA vaccination is currently being researched. TLRs and RIG-I-like receptors are two types of RNA sensors found in humans [124]. Dendritic cells, macrophages, and monocytes all express TLR3, whereas macrophages express TLR7, TLR8, and TLR9. TLR3 recognizes both dsRNA and sRNA (ssRNA). TLR7 recognizes both dsRNA and ssRNA, whereas TLR8 recognizes only ssRNA [125,126]. The RIG-I family includes RIG-I, MDA-5, and LGP2. RIG-I boosts interferon production by recognizing sRNA and dsRNA [127,128]. MDA5 is a cytosolic RNA sensor that detects viral RNA replication's long double-stranded RNA. IRF-3 and NFKB are activated by the discovery of ds RNA, resulting in an increase in IFN-I production [129,130]. The in vitro transcribed mRNA, injection route, and delivery vehicle all play a role in interferon (IFN) induction using mRNA vaccines [131]. After mRNA immunization, pattern recognition receptors (PRRs) are activated, and type I IFN production is increased. Depending on whether the immune response is activated or mRNA translation is blocked, IFN production can be positive or negative [132].

Safety & Drawback:

Vaccines are only given to healthy people, and the safety criteria for current preventive vaccines are extremely stringent. Because it does not require hazardous chemicals or cell cultures that could be contaminated by adventitious viruses, mRNA synthesis avoids the common dangers associated with other vaccination platforms, such as live virus, viral vectors, inactivated virus, and subunit protein vaccines. Furthermore, because mRNA is produced quickly, contaminating bacteria have few opportunities to enter. Infection or vector integration into host cell DNA aren't a concern for mRNA in people who have been vaccinated. mRNA vaccines are thought to be a generally safe vaccination formulation for the reasons stated above. Several different mRNA vaccines have now been tested in phase I to phase IIb clinical trials and found to be safe and well tolerated. In recent human trials, however, many mRNA systems have shown moderate to severe injection site or systemic responses [133, 134].

An adverse event (AE) is a reaction that a medicine or chemical molecule causes that is unplanned or unwanted that occurs during clinical use [135]. Since the COVID-19 vaccines were created utilizing cutting-edge technologies, post-marketing surveillance is crucial for identifying uncommon or enduring side effects. Serious AEs may result in hospitalization, permanent impairment, conditions that are life-threatening, or even death. According to research study stating that A small number of healthcare workers who had received the COVID-19 vaccination visited the emergency department and needed hospitalization [136]. According to earlier research, the most frequent adverse reactions (AEs) caused on by the COVID-19 vaccinations are discomfort at the injection site, fatigue, fever, and muscle soreness [136, 137, 138, 139]. The cause of any adverse effects or responses to the mRNA-1273 vaccination is yet unknown. Anaphylaxis (signs of difficulty breathing, swelling of the face and neck, rash, and low blood pressure) is thought to occur in 2.5 cases for every

million doses of the mRNA1273 vaccine, according to the CDC estimates [140]. A total of 113 deaths were documented, including 78 among LTCF patients and 35 among non-LTCF residents, according to the "Morbidity and Mortality Weekly Report" from the first month of COVID 19 vaccine safety monitoring by VAERS. 19/35 of these non-LTCF residents died after receiving the mRNA-1273 vaccination, according to reports (54.3 percent) [141].

The examinations remain in ongoing, however the underlying chronic diseases such as heart disease, cancer, stroke, suspected pulmonary embolism, and otherwise poor health were deemed to be the causes of death. The prevalent adverse effects to the mRNA vaccinations, such as fever, nausea, and diarrhoea, may have led to death results in some of the vulnerable patients [141]. Reports of deaths brought on by these vaccines are illogical, and as of right now, it is impossible to draw any conclusions. Studies and reports from the observation of hospitalized and elderly recipients, however, point to a mortality of between 0.3% and 0.5%. Despite the fact that the death rate in such cohorts is high, these figures do not provide direct evidence [142, 143]. Therefore, we advise adhering to the CDC recommendations that every vaccine recipient be watched for at least 15 minutes after receiving the shot, with epinephrine readily available at the injection site in case it's required. The CDC advises against administering any of the two mRNA COVID-19 vaccines to those who have previously experienced allergy to polyethylene glycol (PEG), PEG derivatives, or polysorbate [144].

CONCLUSIONS AND FUTURE PROSPECTS

mRNA vaccines are currently seeing a surge in basic and clinical development. Hundreds of preclinical and clinical publications demonstrating the efficacy of these platforms have been published in the last two years alone. While most early research on mRNA vaccines focused on cancer, a number of subsequent studies have showed the effectiveness and adaptability of mRNA to protect against a wide range of infectious infections, including influenza, Ebola, Zika, Streptococcus spp., and T. gondii. While preclinical research has raised hopes for the possibilities and benefits of mRNA-based vaccinations, two recent clinical reports have cast doubt on those hopes [133,134]. In both studies, immunogenicity in humans was lower than expected based on animal models, a characteristic that has also been observed in animal models. The same thing happened with DNA-based vaccines [145], and the adverse effects were not insignificant. We stress that these trials only look at two different mRNA vaccination platforms, and there could be significant differences if the vaccine's expression and immune stimulatory characteristics are modified. More research is needed to establish how different animal species respond to mRNA vaccine components and inflammatory signals, as well as which immune signaling pathways in humans are most successful. Recent developments in understanding and lowering innate immune detection of mRNA have assisted efforts not just in active vaccination but also in a variety of passive immunization and passive immunotherapy applications for infectious illnesses and cancer. Comparisons of different mRNA expression platforms should reveal which systems are best for passive and active immunization. Given the wide number of potential mRNA platforms on the market, more head-to-head comparisons would be extremely beneficial to the vaccination industry, allowing researchers to focus their efforts on the platforms that are most suited for each application. Without important recent developments in the areas of innate immune detection of RNA and in vivo delivery technologies, mRNA vaccines would not have progressed as quickly as they have. Extensive basic research into RNA, lipid, and polymer biochemistry has enabled the translation of mRNA vaccines into clinical trials, resulting in a staggering

amount of money being invested in mRNA vaccine firms [145].

Moderna Therapeutics, which was launched in 2010, has raised about $2 billion in funding with the goal of commercializing mRNA-based vaccines and treatments [146,147]. Moderna's clinical assessment of a potential nucleoside-modified mRNA vaccine for Zika virus has received assistance from the US Biomedical Advanced Research and Development Authority (BARDA) (NCT03014089). CureVac AG is developing an innovative approach to tailored cancer therapy using mRNA vaccines in Germany, and BioNTech is developing an innovative approach to personalized cancer medicine using mRNA vaccines [148]. The results of recent examinations imply that the emergence of resistant SARSCOV2 mutations current COVID19 vaccines ineffectively.

In contrast, vaccines COVID19 may cause both neutralizing antibodies and SARSCoV2 CD4 + CD8 + T-Cell-specific responses, CD4 + and CD8 + and CD8 + specific TCELL and CD8 + and CD8 + after vaccination with a variety of vaccine platforms were observed [149]. Since many blazing epitopes are dispersed by viral proteins, while the neutralization of antibodies is directed to a limited part of the viral protein, the evading of T-Cell responses is theoretically more difficult than the evading neutralizing antibody responses [150]. Although SARSCoV2 mutations have been reported to prevent the virus from being linked to the main histocompatibility complex, Tarke et al. SARS-CoV-2 variants had no effect on CD4+ and CD8+ T-cell responses in COVID-19 convalescents and recipients of COVID-19 mRNA vaccines, according to a recent study. T cell responses to SARSCoV2 variants B.1.1.7, B.1.351, P.1 and CAL.20C (which emerged in Southern California) were similar to those of the ancestor strain. Despite changes in variations, the majority of SARSCoV2 T cell epitopes remained conserved [151]. The marketing of personalized GMP products of companies such as New England Biolabs and Aldevron175 has accelerated the transition from basic research to clinical trials Finally, the coalition for epidemic preparatory innovations (CEPI), which has just initiated, gives the reason for trust in future responses to immediate viral epidemics. This public-private partnership intends to generate $1 billion to create platform-based vaccinations, such as mRNA, to quickly address emerging outbreaks before they become uncontrollable [152]. As a result, the future of vaccines with mRNA is very bright, and the clinical data as well as the resources provided by these companies are considerably expected by these companies and other institutions and the fundamental research in mRNA-based treatments considerably.

Funding Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare that they have no conflict of interest in this study

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How to cite this article: Rashmi Subramanian, Prabhu Meganathan, Raja Selvarajan. mRNA vaccine - game changer against infectious disease. *Int J Health Sci Res.* 2022; 12(7):250-270.
DOI: *https://doi.org/10.52403/ijhsr.20220737*

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