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mRNA Vaccines: Transforming Disease Prevention for the Modern Era

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ABSTRACT

Messenger RNA (mRNA) vaccines have completely changed the area of immunology by providing a novel approach to disease prevention through their rapid development and potent immune responses. The introduction of mRNA vaccines was propelled into the spotlight with the international effort to combat the COVID-19 epidemic, where they showcased their potential in public health. These vaccines utilize synthetic mRNA that encodes a viral protein, typically a spike or antigen, which, when introduced into the body, prompts cells in order to generate the corresponding peptide. This peptide is then recognized by the defense mechanism, which mounts an immunological reaction and establishes memory, enabling the body to swiftly combat the actual pathogen upon future exposure. Designing an mRNA vaccine involves encoding the viral protein in a stabilized form of mRNA, ensuring that it is capable of efficiently entering cells and eliciting a strong, durable immune response. Development has focused on optimizing these delivery systems and ensuring the stability of the mRNA. The primary applications of mRNA vaccines extend beyond COVID-19 and include the safeguard of various infectious diseases including influenza, rabies, and Zika virus. Additionally, mRNA vaccines are being explored in cancer immunotherapy and autoimmune disease treatment. In this review, we summarize about their design and development, mechanism of action, prevention of diseases, safety profile and their applications.

Keywords: mRNA, covid-19, vaccines, immune, infectious diseases.

INTRODUCTION

The best defense against the spread of both infectious and non-infectious diseases for humans is vaccination. Because vaccination reduces the cost of treating infectious diseases, it has a significant positive economic impact on the healthcare system. Furthermore, vaccinations can lessen the effects and danger of epidemics [1]. Many years ago, the idea of genetic (DNA and RNA) vaccines was floated, with the expectation that a safe, effective, adaptable, and simple-to-manufacture vaccine class could be created. The creation of mRNA sequences, the development of techniques enabling the easy, quick, and three developments represent the most important advances in mRNA vaccine technology in recent years: large-scale cGMP mRNA synthesis; and the development of highly efficient and secure mRNA vaccine delivery materials. [2].

The molecule was first commercialised in 1989 after an extensively utilised in vitro

transfection technique was developed, despite its vulnerability to the nearly universal ribonucleases (RNases). The use of mRNA as a vaccination platform was pushed only a few years later. It might be perfect because it combines the immunological features of live attenuated vaccines—such endogenous antigen expression and T cell induction—with those of dead or subunit vaccines, including defined composition and safety. [3]. Nonetheless, the early 1990s saw the first experiments with the therapeutic effects of directly expressing foreign mRNA molecules in host animals, murine muscle cells were exposed to RNA vectors that encode reporter genes, such as luciferase and β-galactosidase, and rats were transfected with vasopressin mRNA to reverse Diabetes-Insipidus. Later, it was shown that applying mRNA in vivo activated B cells' humoral response to make certain antibodies as well as cytotoxic T cells [4].

mRNA vaccines have shown considerable promise in the fight against cancer and other incurable diseases due to their exceptional performance against COVID-19. Yet, a number of variables still have a significant impact on antitumor immunity and mRNA stability. These include, among other things, organ-selective targeting, elevated mRNA endosomal escape through delivery platform design, and neoantigen screening and identification [5]. They overcome constraints connected to particular histocompatibility leukocyte antigen molecules to alter the body's biological processes in order to create antigens, trigger immune responses, and suppress malignancies [6]. These new mRNA vaccines have a lot of potential advantages over the more established live attenuated entire virion and DNA-based viral vector vaccines. They are safe because, in contrast to live attenuated vaccinations, they are not contagious and do not integrate, unlike vaccines based on DNA-based viral vectors. mRNAs are readily scalable to kilogramme level quantities due to their ability to be produced with high yields at low cost by in vitro transcription operations. As such, there's no chance of infection or insertional mutagenesis, they work incredibly well, and many of them come in stable, highly translatable forms [7].

These days, several preclinical and clinical investigations have shown that enormous potential of mRNA vaccinations against a variety of diseases, including autoimmune encephalomyelitis, malignancies, infectious diseases which includes influenza A, Zika virus disease, coronavirus disease 2019 (COVID-2019), rabies, and more [8]. In vivo mRNA delivery can be achieved by a variety of delivery mechanisms based on lipids, polymers, and exosomes. Using lipid nanoparticles (LNPs), the most advanced mRNA delivery system available, the SARS-CoV-2 mRNA vaccination has been implemented [9].

DEVELOPMENT, DESIGN AND DELIVERY SYSTEMS:

Development:

It was noted in a 1990 publication that the direct injection of "naked" RNA might result in the how the encoded protein is expressed in vivo, marking the first demonstration of mRNA as a promising in vivo gene delivery approach. But a number of obstacles prevented the quick use of in vitro generated mRNA as a simple injection technique to generate a protein immunogen in vivo.

Self-amplifying RNA vaccines are a special kind of m RNA vaccine that formerly been developed in pre-clinical settings alongside viral vectors and plasmid DNA vaccines. The goal of this self-amplifying m RNA vaccine is to encode not only the desired antigen but also vital viral replication proteins that come from other viruses, such alpha viruses, as opposed to the target virus. The quick creation of vaccination candidates—which can be created using the targeted antigen and the pathogen's known genetic sequence—is a major factor in the quick acceptance of m RNA technology for COVID-19 therapy. Furthermore, the encoding of the particular antigen still has an impact on the generally uniform manufacturing process for mRNA vaccines [10].

Design:

The idea that ribosomes get genetic information from genes through an unstable intermediary called messenger RNA, which is then translated into proteins by ribosomes, was supported in 1961 by Brenner, Jacob, and Meselson. This theory was first proposed by Jacob and Monod. Currently, the only cell-free process available for creating mRNA therapies is in vitro transcription. In order to facilitate the processing of these antigens into epitopes that can be presented by class 1 and class 2 major histocompatibility complex molecules on the surface of antigen-presenting cells, these mRNA are designed to direct the production of these antigens into particular cellular compartments [11].

Delivery systems:

It is essential that mRNA vaccines are precisely delivered to the target cells in the human body in order for them to be effective. m RNA vaccines should enter into the cytoplasm in order to be adopted into the intended protein as they cannot enter the nucleus. Phospholipid bilayer of the cell membrane which is negatively charged must be crossed by mRNA in order for it to reach the cytoplasm. Since bare m RNA has a very high molecular weight, it requires a carrier for cellular entrance, while molecules with a molecular weight less than 1,000 Da can pass through the cell membrane passively. Viral and non-viral vector delivery systems are the two types in mRNA vaccine delivery technologies [12].

Other delivery methods include peptide-based delivery, cationic nano emulsion, virus-like replicon particles, and electroporation for dendritic cell-based mRNA vaccines [14].

ROUTES OF ADMINISTRATION:

The delivery mechanism for mRNA vaccines is a critical factor in determining the vaccination's overall efficacy. The safety and effectiveness of the vaccine are greatly influenced by the anatomical and physiological features of the vaccination location, which can include the skin, lymphoid organs, or muscle. Vaccines can be given locally or systemically. As with intravenous injections, By injecting the vaccine straight into the bloodstream, systemic delivery allows it to enter the body and impact each and every cell. On the other hand, systemic delivery is often linked with a higher risk of side effects; in contrast, local injections are given directly at the location of action [13].

MECHANISM OF ACTION:

The ultimate goal of all vaccinations is to stimulate the immune system to produce a durable protective response to an antigen. The immune system can obtain the encoded protein from the vaccinee's cells by means of their ability to express it, when the antigenic sequence is introduced into them. That's how mRNA vaccine’s function [14].

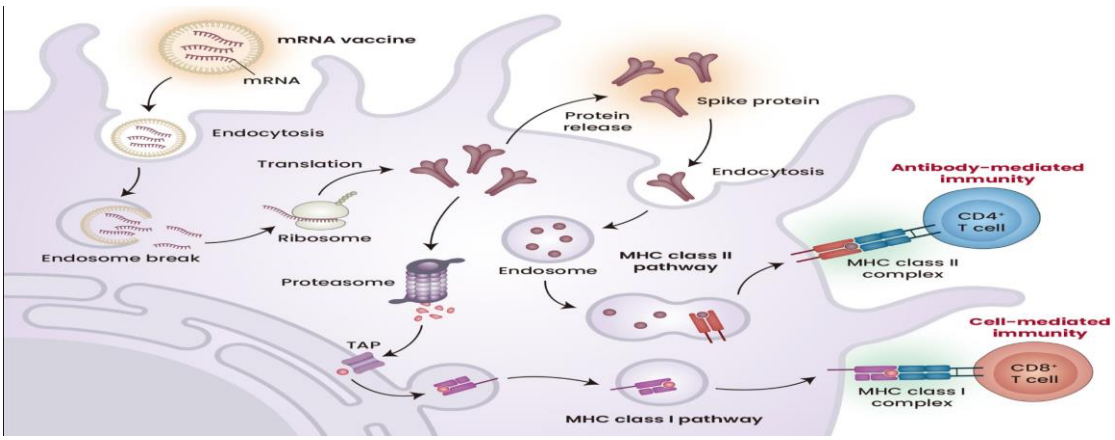

Fig.1 Mode of action of mRNA vaccines (adopted from Sora Son, Kyuri Lee)

The host immune cells produce an immunological response in response to vaccination against these illnesses, mostly through the class II major histocompatibility complex (MHC), which helps the cells recognize the infections as external antigens. On the other hand, the purpose of mRNA vaccines is to encode particular antigens, not complete diseases. Antigen-specific immune responses can only be elicited by the translation of mRNA vaccines into antigens after cell delivery. Translated antigens that are ingested and released by cells as exogenous antigens have the potential to initiate MHC class II-mediated immunity. Furthermore, After the mRNA vaccines are given to antigen-presenting cells, the host recognizes the translated antigens as endogenous antigens. Mostly, this sets up immunological responses related to MHC class I. Higher levels of cellular immunity are frequently obtained from mRNA vaccinations than from inactivated or live-attenuated vaccines because the MHC class I system is linked to CD8+ T-cell-mediated cellular immunity. Effectiveness as a treatment in cancer immunotherapy is determined by the ability of cancer vaccines to elicit tumour antigen-specific cellular immunity, specifically antigen-specific cytotoxic T-cell immunity [15].

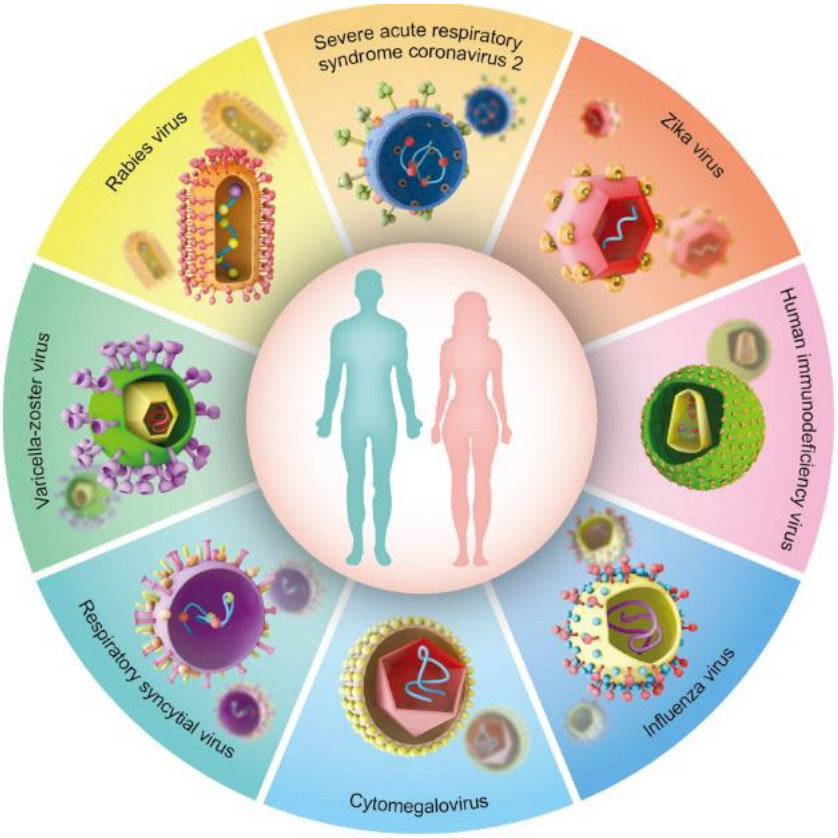

Fig.2 Infectious illness landscape for mRNA vaccines (adopted from Gang Zhang et.al)

It has been demonstrated that precise targeting to deliver mRNA or nanoparticles to certain cells can elicit strong effector and memory T-lymphocyte responses in addition to robust IFN-α-mediated eradication of advanced cancers. Tumor-associated antigens (TAAs) expressing mRNA or total tumour RNA (TTA) can be transfected into dendritic cells as part of cancer immunotherapy [16].

EFFECTIVENESS IN DISEASE PREVENTION:

Treating rare genetic disorders should benefit greatly from the ability to therapeutically alter mRNA expression. Unfortunately, there are a number of issues with this treatment

method, including as the brief half-life of mRNA injected externally and the ensuing synthesis of proteins. Untranslated region (UTR) modification is one method in order to increase translation effectiveness and mRNA stability [17]. The remarkable safety overview of mRNA vaccinations is one of its main benefits. Since mRNA vaccinations refuse to merge with the host genome like DNA-based medicines do, the possibility of insertional mutagenesis is eliminated. Antigen stimulation is brief due to the transient nature of mRNA production, hence reducing the likelihood of autoimmune reactions or chronic inflammation. Furthermore, the speed at which mRNA vaccines may be designed and synthesized allows for quick reactions to changing oncological difficulties, such as tailoring vaccinations to each patient's specific tumor features, which represents a major advancement in individualized cancer therapy [18]. Numerous mRNA vaccinations are now undergoing clinical testing. and are expected to treat novel and recurring infectious illnesses. Recently, The COVID-19 mRNA vaccine's successful implementation demonstrated the platform's advantages and paved the path for the application of mRNA vaccines in the prevention of infectious diseases.[19].

Influenza viruses:

Influenza viruses belong to the family Orthomyxoviridae and are primarily classified into four varieties: A, B, C, and D. Of these, strains A and B have a clinical relationship with problems in humans. The glycoprotein haemagglutinin (HA) on the surface of the virus is typically the focus of the mRNA vaccination against influenza viruses because it facilitates viral entry. However, because the influenza virus is rapidly changing due to antigenic drift, the HA antigen component of the mRNA vaccine requires annual study and modification. [20]. Worldwide, influenza viruses are thought to be the cause of between 290,000 and 650,000 deaths each year. Inactivated influenza viruses raised in chicken eggs are used in conventional influenza vaccinations, which have lengthy production durations and challenging purifying processes. Moreover, in order for the viruses to thrive as best they can in chicken eggs, they change, occasionally making them ineffectual in humans. For instance, low efficacy in the 2016–2017 season was linked to the removal of a glycosylation site in vaccines produced in eggs [21]. created mRNA vaccines to immunise against the influenza A, H3N2, and H5N1 viruses. These vaccines were administered intradermally to mice, ferrets, and domestic pigs, and their immunogenicity and/or protective effectiveness were evaluated in animal models [22]. Although egg-based platforms are used to create the majority of influenza vaccines, there are also vaccinations that use platforms based on cell culture and recombinant proteins [23]. A faster time to market for an mRNA platform enables the removal of host adaptation and egg dependence, as well as the gathering of more data prior to strain selection. Additionally, an mRNA platform offers an adaptable manufacturing schema that may be used with in silico designs that promise increased immunisation coverage and efficacy [24].

SARS-CoV-2:

Serious acute respiratory syndrome-2 virus (SARS-CoV-2) is the extremely contagious respiratory virus that is the cause of the present global coronavirus disease 2019 (COVID-19) pandemic. In the initial year of the pandemic, more than 100 million people globally have contracted the novel coronavirus disease 2019 (COVID-19). Attaining worldwide herd immunity is essential to limiting the pandemic, as the death toll in the United States alone has surpassed 500,000. This suggests that in order to develop active immunity against the SARS-CoV-2, at least 70–80% of the population must do so, either by vaccination against SARS-CoV-2 or as a result of a prior COVID-19 [25].

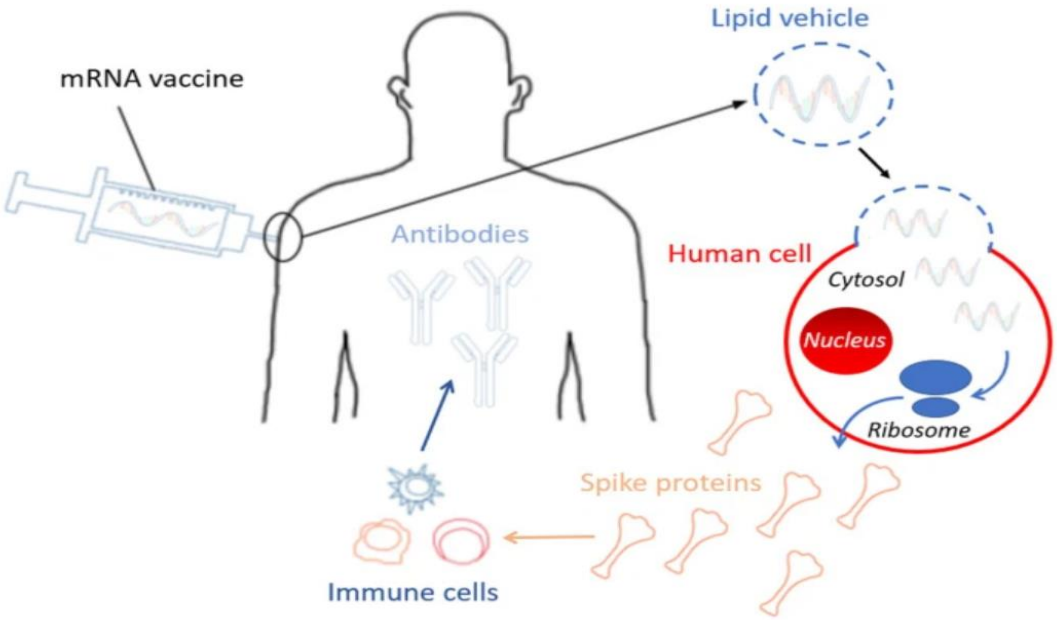

Fig.3 mRNA vaccination mechanism-COVID-19 (adopted from Pratibha Anand et.al)

As of December 2020, the US Food and Drug Administration has linked the effectiveness of the Zika immunisation to neutralising antibodies (nAbs), which are important mediators of protection against flavivirus infections. In order to avoid the coronavirus sickness 2019 (COVID-19), which is brought on by an infection with the SARS-CoV-2 virus, the administration authorised the use of two in an emergency vaccination (EUA). December 11th will see the release of the BNT162b2 vaccine by Pfizer-BioNTech, and December 18th will see the release of Moderna's mRNA-1273 vaccine. Both mRNA vaccines are currently licensed [26].
Since the full-length S protein, S1, and RBD can trigger T cell-mediated immunity and very powerful neutralizing antibodies, they have been identified as prospective targets for the creation of a coronavirus vaccine. Recent research has also shown that, in Immunisation with the recombinant RBD of SARS-CoV-2 produced high titers of reducing antibodies in the absence of antibody-dependent enhancement (ADE) of infection. We now know more about this vaccine target thanks to the quick and high-resolution resolution of the structures of the RBD-ACE2, RBD-SARS-CoV-2 RBD, and RBD-monoclonal antibody complexes. The ability of the mRNA vaccine platform to expand production quickly is one of its main benefits, which makes it especially desirable for responding to the pandemic [27].

Zika virus:

In addition to numerous other mosquito-borne viruses of clinical importance (such as DENV, WNV, and yellow fever virus [YFV]), the Zika virus is a positive-sense single-stranded RNA virus belonging to the Flaviviridae family. Spondweni virus is the sole other member of its clade and its closest relative. Infections with the Zika virus typically cause subclinical or moderate influenza-like symptoms, but there have also been reports of more serious symptoms, such as adult Guillain-Barre syndrome and microcephaly in infants whose mothers have the virus. Zika virus prevention is the main emphasis of the public health response because there is now neither a vaccine nor a viable therapy for the virus, especially not for pregnant women [28]. It was initially isolated in 1947 in Uganda, Africa. [29].
The success of the Zika vaccination has been associated with neutralising antibodies (nAbs), which are significant mediators of protection against flavivirus infections. ZIKV strain Brazil SPH2015 pre-membrane and envelope (prM-E) glycoproteins are encoded by this mRNA vaccine candidate,

which is encased in lipid nanoparticles. It's interesting to note that while ZIKV prM–E mRNA-LNP given twice induced strong protective immunity, it only protected against a fatal dosage of ZIKV [30].

Cancer:

One of the main causes of death worldwide is still cancer, accounting for almost 10 million deaths annually. Discovering efficient ways to combat cancer has been a top priority for scientists around the globe for many years, yet there are still many obstacles in our way. In recent times, immunotherapy has emerged as a major modality for treating cancer. Cancer vaccines target TAs specifically in order to elicit humoral and cellular immune responses that impede the growth of tumours and ultimately eradicate them. TAs fall into two categories: tumor-associated and tumor-specific antigens. Tumor-associated antigens are nonmutant proteins that exhibit aberrant or overexpressed expression in cancerous cells. Tumor-associated antigens include differentiation antigens, oncoviral antigens, silent gene products, and universal tumour antigens. There has been little progress in the clinical testing of cancer vaccinations that target tumor-associated antigens. Tumor-associated antigens can occasionally be expressed in healthy cells, raising the possibility of autoimmune damage from vaccinations. Normal cells typically do not express tumor-specific antigens, which are only expressed by tumor cells. mRNA vaccines are a potent and appealing immunotherapeutic platform against cancer due to their high potency, specificity, adaptability, ability to develop quickly and extensively, potential for low-cost manufacturing, and safety [31]. Four categories of cancer vaccines exist: vaccines based on tumours or immune cells, vaccines based on peptides, vaccines based on viral vectors, and vaccines based on nucleic acids. Nucleic acid-based vaccinations (DNA or RNA) have great promise for a number of reasons. Recently, messenger RNA (mRNA) vaccine has become a viable alternative to DNA vaccine for the prevention of infectious diseases and the development of anti-cancer treatments [32].

There are many commonalities throughout mRNA vaccines. Upon entering the cytoplasm, mRNA can undergo direct translation into proteins, in contrast to viral vectors and plasmid deoxyribonucleic acid (DNA), which can cause mutations through gene insertion and/or infection. mRNA vaccines are safe, nonintegrated, and noninfectious because of these factors. Because of the flexibility and diversity of the units encoded in an mRNA transcript, both immunomodulatory and antigenic molecules can be encoded to trigger and modify both innate and adaptive immune responses [33].

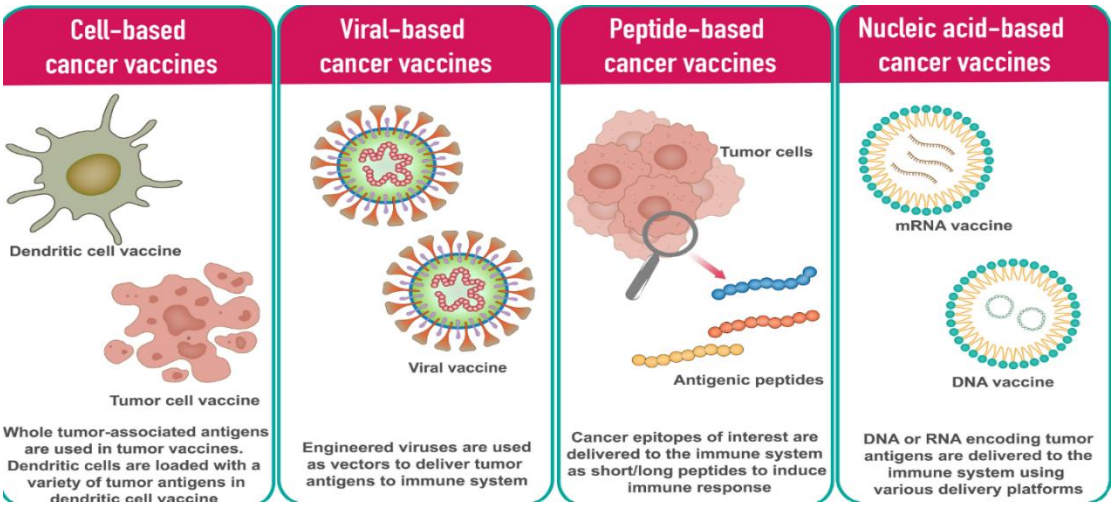

Fig.4 Various platforms for cancer vaccines. (adopted from Yashavantha L. Vishweshwaraiah et.al)

SAFETY PROFILE:

Common side effects:

When it comes to vaccination receivers, the incidence of moderate local reactions—such as warmth, discomfort, redness, and swelling—is higher than it is for placebo recipients. Additionally, the vaccinated group experienced a higher frequency of systemic adverse effects compared to the placebo group, with the majority appearing one to two days after immunization. These side effects included fatigue, fever, headaches, muscle soreness, and joint pain.

Local reactions:

The majority of these local reactions lasted one to two days and were categorized as mild to moderate in intensity. Remarkably, less than 1% of participants in all age groups reported being in severe pain.

Systemic reactions:

There were more side effects recorded after the second dosage of the immunisation than after the first. Once the second dose was taken, the most commonly reported side effects were fatigue and headache.

Adverse events:

The serious side effects from the vaccination that were recorded, including right axillary lymphadenopathy, paradoxical ventricular arrhythmia, right leg parasthesia, and a shoulder injury connected to the shot. Additionally, reports of Bell's palsy have been made, an idiopathic disorder affecting cranial nerve 7, which is an acute, transient, unilateral peripheral facial paralysis [26]. Other side effects include myocarditis, pericarditis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and cerebral venous sinus thrombosis [34].

Mortality:

The COVID-19 vaccine caused myocarditis in some people who got it, according to reports made by THE VACCINE ADVERSE EVENT REPORTING SYSTEM in April 2021. Researchers examined death certificate data from Oregon from June 2021 to December 2022 for people aged 16 to 30 years in order to evaluate the risk of unexpected cardiac death in young adults and adolescents following COVID-19 vaccination. Three of the 40 recorded deaths among recipients of the m RNA COVID-19 vaccine occurred within a hundred days after the injection. Of these cases, the cause of death was unknown for one person, and two included people with pre-existing medical issues [35].

APPLICATIONS OF mRNA VACCINES:

Globally, preventive vaccinations against diseases remain a top focus. Most human vaccines currently in use are known to work primarily by neutralizing antibodies to provide protection against disease, not by infecting. More complex vaccination formulations will often be needed to induce comprehensive immune responses that include both production and CD8+ and CD4+ T cell activation [36].

The use of mRNA-based medicines is anticipated to cure a wide range of illnesses that are resistant to existing therapies, including cancer, infectious diseases, metabolic genetic abnormalities, heart problems, cerebrovascular diseases, and more.

These mRNA drugs come with a number of advantages, such as easy production methods, little side effects, and great efficacy. Notably, mRNA vaccines have been shown to be both effective and safe in stopping the spread of COVID-19.

The focus of recent studies on m RNA vaccines has been on determining how well they work to protect against various infectious diseases, including new COVID-19 variants and the influenza, respiratory syncytial, zika, rabies, ebola, and streptococcus species viruses [37].

The development of both innate and adaptive immune responses is a crucial element of vaccine effectiveness, and the mechanism of action of mRNA vaccines is in line with this notion. Like live-attenuated vaccinations, mRNA vaccines induce localised inflammation at the injection site to attract antigen-presenting cells and facilitate the production of antibodies that neutralise the

infection. Dendritic cells (DCs) are key players in inducing immunological responses and are very responsive to mRNA transfection. They effectively supply complete antigens to B cells, encouraging an immune response mediated by antibodies. Immunotherapy may be improved by loading full-length tumor antigens onto dendritic cells, which can elicit widespread T-cell responses regardless of the patient's human leukocyte antigen (HLA) type. The efficacy of mRNA vaccines against SARS-CoV-2 has spurred scientific curiosity in the possibility of using mRNA vaccine technology to create an HIV vaccine. With 39 million people living with HIV and 630,000 recorded deaths in 2022, HIV remains a major global public health risk even after decades of intensive research. The two main approaches to HIV prevention and treatment at the moment are antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) [38].

CONCLUSION

mRNA vaccines are a promising tool in modern medicine, offering effective, safe, and adaptable prevention strategies for infectious diseases and beyond, with the potential to revolutionize both public health and personalized medicine. It is administered directly into the blood stream with IV route, precisely delivered to the target cells in the human body in order for them to be effective. mRNA vaccines introduce a genetic code for a pathogen's protein, prompting cells to produce it and trigger immunity. Despite concerns about long-term effects and initial hesitancy, extensive studies have shown mRNA vaccines to be safe and effective. Their quick development and adaptability may pave the way for future vaccines, potentially targeting a wide range of diseases, transforming vaccine science for years to come. The versatility and rapid development capabilities of mRNA vaccines suggest a bright future. Continued investment in research and development could lead to revolutionary treatments and preventive measures, transforming the landscape of medicine and public health.

As research continues to advance, we can expect to see: Improved delivery systems and formulations, Enhanced immune responses and duration of protection, Expanded applications beyond infectious diseases, such as cancer and genetic disorders, Integration with other technologies, like nanotechnology and artificial intelligence, Increased global access and equity through decentralized production and distribution.

While challenges remain, the potential of mRNA vaccines to shape the future of healthcare is undeniable. Continued investment, innovation, and collaboration will be essential to realizing their full potential and creating a healthier world for generations to come."

Declaration by Authors

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