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Moderna (mRNA-1273) Covid-19 Vaccine, "A Systematic Review"

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Abstract

A Global pandemic, declared by WHO, caused due to a deadly virus known as a "SARS-Cov-2", has resulted in 4.3 million deaths. Its RNA based genome and lack of proofreading ability has made this virus more prone to get the frequent mutations and results in the formation of new variants and increased pathogenicity. Scientists had been trying hard to develop the ways through which this lethal virus could be eradicated, from the day the genome of SARS CoV-2 was first reported. In order to prevent from this viral infection more than 90 vaccines were developed but few of them were approved by FDA for the human trials. Moderna Inc came up with "mRNA-1273" vaccine which was given EUA approval on 18th December, 2020 by the FDA. The vaccine is based on active mRNA, translated into spike proteins of virus, is developed by the help of nanotechnology. The clinical trials have proved an efficacy of 94.1%. Moreover, the vaccine is able to prevent disease caused by the alpha, beta, gamma and delta variant of SARS-Cov 2 in recent studies. In this review article the composition, technology, mode of action, immune responses, clinical trials and efficacy as well as the comparison of moderna vaccine with other available covid-19 vaccines has been discussed.

Keywords: Covid-19; mRNA based vaccine; Moderna (mRNA-1273); Mode of action; delta variant; Immune responses; Clinical Trials; Efficacy.

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1. Introduction

Since the end of 2019, the world has been caught up by a deadly life threatening virus "Coronavirus", that was declared by World Health Organization (WHO) as a cause of Pandemic [1]. It has wide scale global effects due to which the world has faced drastic consequences [2]. The SARS-CoV-2 depicts the 50% of genome homology with the MERS-CoV and 79% with SARS-CoV. The reason of rapid spread of SARS-CoV-2 as compared to the SARS-CoV can be cleared by the structural differences in the S proteins among the "coronaviruses" [3]. Back in 2003, the SARS-CoV epidemic vanished without invading the whole world and that was why, no any vaccine was required [4]. But COVID-19 didn't disappeared like SARS because of its swift global transmission. Genetic variants of this lethal virus are continuing to emerge since 2019, when the SARS-CoV-2 was first reported. This has complicated the strategies to eradicate COVID-19 [5]. Variants of SARS-CoV-2 and their origin of identification are listed in (Table 1). Each new variant has an increased transmission rate than the older variant.

Table 1: Variants of covid 19 and their country of origin [6]

Variant	First identified
Alpha - B.1.1.7	United Kingdom
Beta - B.1.351	South Africa
Gamma - P.1	Japan/Brazil
Delta - B.1.617.2	India

The two basic approaches for the treatment of Covid-19 are antiviral pharmaceuticals and immunotherapies [7]. The most promising approach to eliminate the virus are vaccines [8]. Generally, the old methods of developing stable and effective vaccines are inactivated virus, DNA-based or protein-based [9, 10]. But recently, a better preventive approach i.e., mRNA-based vaccines is developed which is easier to produce, is more efficient and is safer [11]. Due to the rapid spread of COVID-19, mRNA-based vaccine development seems to be an approach to prevent infection and to prevent a second wave of this pandemic [12]. Vaccines which are approved or are in clinical trials, their method of production and efficacy is shown in (Figure 1). Normally a vaccine requires a minimum of (12 to 18 months) to develop, by using the conventional method for vaccine development, trials, and approval [13]. This whole process requires time for the production of effective vaccine in this time of pandemic. In order to prevent from this lethal viral infection different companies started making different type of vaccines and many of the vaccines were given the approval for the human trials as well. Nonetheless as the sequence of the genome of SARS-Cov-2 was released in early January 2020, within the tenure of three months "Moderna" initiated its clinical trial for its mRNA based vaccine in March, 2020. It is the first time ever the mRNA based vaccines were used for the human trials for preventing the SARS CoV-2 infection. This article aims to describe the development of Moderna mRNA-1273 vaccine for SARS-CoV-2, mode of action, immune responses, clinical trials and efficacy.

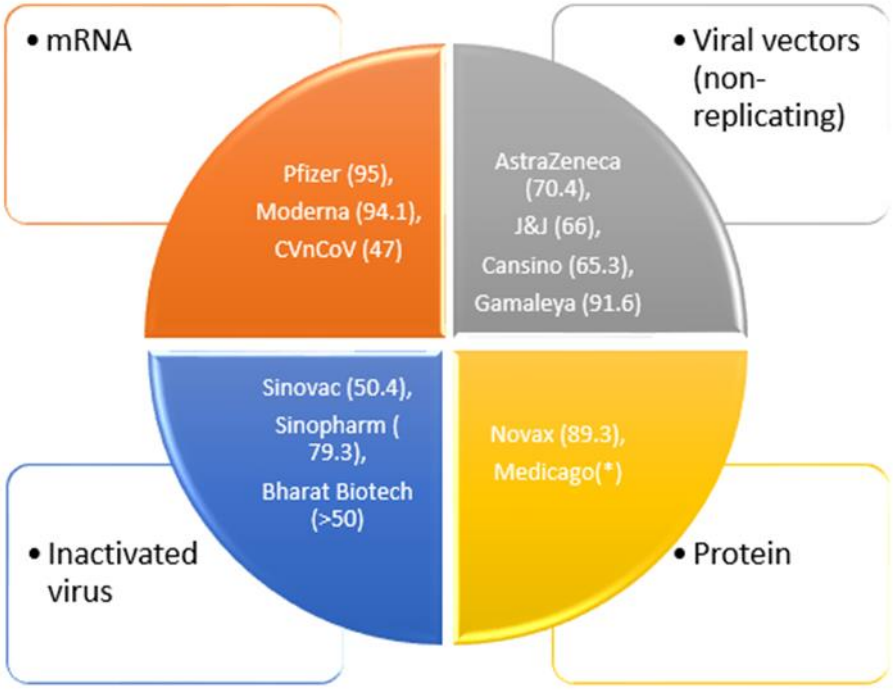

Figure 1: Different type of vaccines and their efficacy

2. Messenger RNA based vaccines

Every year, a number of lives are saved from millions of diseases by the help of vaccines. Various techniques are in use for the formation of vaccines. The traditional methods use live weakened pathogens, inactivated pathogens, their subunit or proteins to provide protection against the disease. These vaccines helped in the control and eradication of "polio, small pox, measles, rubella and mumps". Although these conventional vaccines are successful still there are obstacles to develop vaccines against deadly pathogens, especially those which can take over the adaptive immune response. These vaccines approaches are not successful in case of emerging viruses because they need time for development and large scale production [14]. Messenger RNA-based vaccines came forward to revolutionize the field by solving current developing challenges and offering novel vaccine formulation [15]. RNA is a highly unstable molecule due to the ubiquitous presence of ribonucleases (RNases), that's why it's therapeutic is considered as a controversial idea. In 1989, after the development of successful in vitro transfection technique mRNA was first introduced as a therapeutic. Later two years, mRNA was prescribed as a vaccine, it is considered ideal because it combines endogenous antigen expression and T cell induction like features of live attenuated vaccines and defined composition and safety like features of killed or subunit vaccine. The mRNA vaccine is more efficient because they do not need to travel across the nuclear membrane as compared to the DNA- based vaccines as in (Figure 2). The mRNA-based vaccines are translated within the cytoplasm and are converted to proteins. Moreover, mRNA binds to pattern recognition receptors. The mRNA vaccines may be designed to be self-adjuvanting, a feature which protein-based vaccines lack [16]. Two mRNA-based vaccines BNT162b2 and mRNA-1273 are first, which are historically given the approval for emergency use in less than a year, since Covid-19 outbreak and another mRNA vaccine, CVnCoV is in third phase of clinical testing [17].

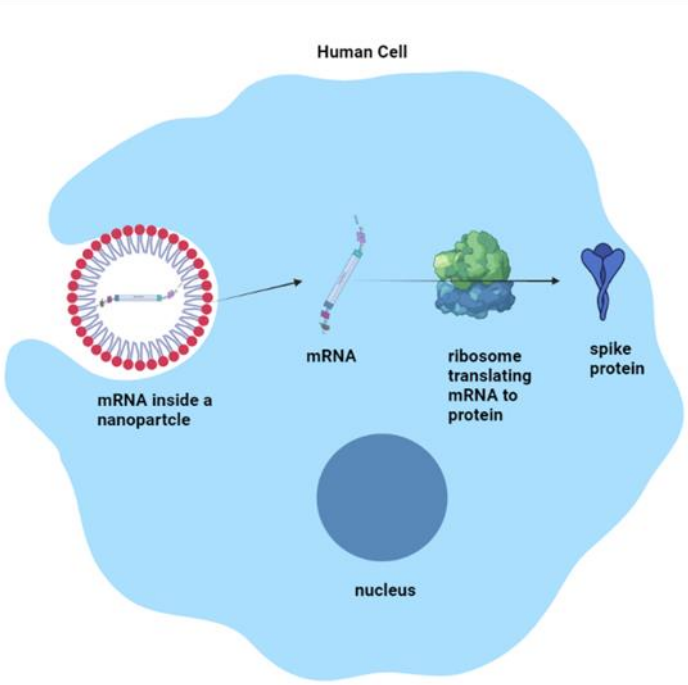

Figure 2: mRNA being translated into spike protein (created in https://biorender.com/)

3. Moderna Company

A huge biotechnology company Moderna Inc was founded in 2010 and is situated in Cambridge, United States [18]. The company had a capital of US$2.561 billion and revenues of $803 million by the end of the 2020 financial year [19]. Moderna Inc specialty is to develop vaccines by utilizing the messenger ribonucleic acid (mRNA) technology. The company focuses majorly on six areas in therapeutic development which are systemic secreted therapeutics, cancer vaccines, intertumoral immmuno-oncology, localized regenerative therapeutics, intracellular therapeutics and prophylactic vaccines. The biggest achievement of the company is the development of the "COVID-19 vaccine" named as "mRNA-1273"[20].

4. Formulation of vaccine

There are four major structural proteins of SARS-CoV-2 (Figure 3). One of the most necessary structural proteins required for the entry of the virus inside the cell. This spike protein is actually a 1273 amino acid (hence the name of vaccine mRNA-1273 is based on this fact) has two major sub-domains which are named as S1 and S2 (Figure 4). The S1 domain has the receptor binding domain or RBD and helps in the binding of the virus to the angiotensin-converting enzyme 2 or ACE2 receptor (Figure 3). The S2 harbors the fusion peptide and enable in the successful entry of the virus [21]. The 986 and 987 residues of the S protein were substituted with 2 prolines following the release of the genome of Sars cov 2. These residues are basically mutated to facilitate the analysis of structure as well as the formation of serological assays. Moderna has developed the vaccine for sars cov 2 by mutating the spike protein with 2P and then enclosing this mRNA inside the nanoparticles made of lipids [22].

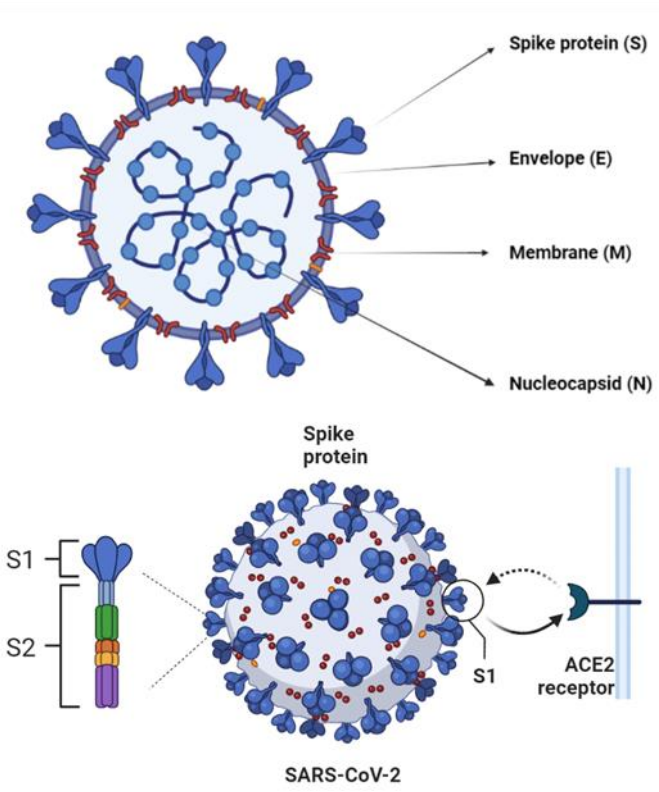

Figure 3: Structure of Covid-19 and binding of spike protein with ACE2 receptor (Created in https://biorender.com/)

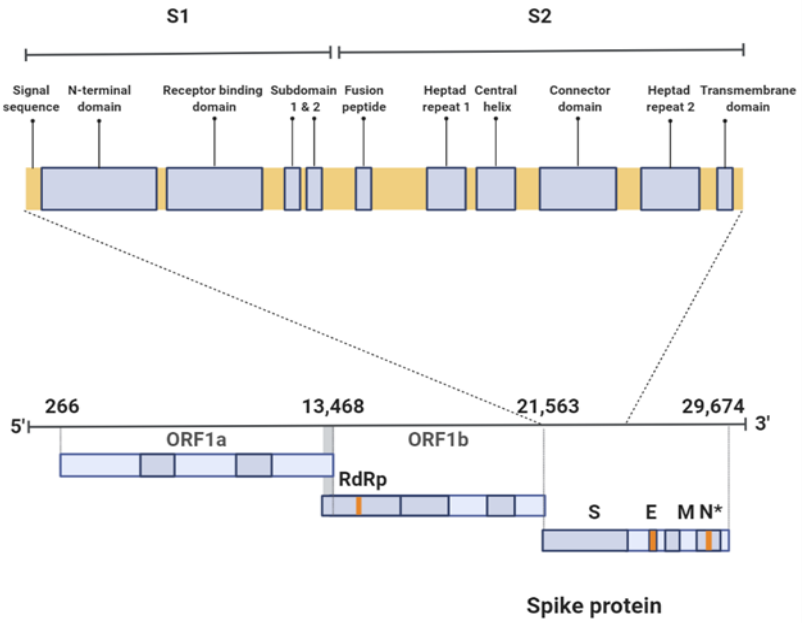

Figure 4: Genome of spike protein of Covid-19 (Created in https://biorender.com/)

5. Technology

The technology used to make the mRNA in this vaccine is nanoparticle delivery system and this technology

played a huge role in the success of the mRNA-1273 (Figure 5). These nanoparticle delivery system proficiently helps to proficiently deliver the mRNA inside the cell following the intramuscular route of administration. These nanoparticles also function as an adjuvant and in the reactogenicity of the vaccine [23].

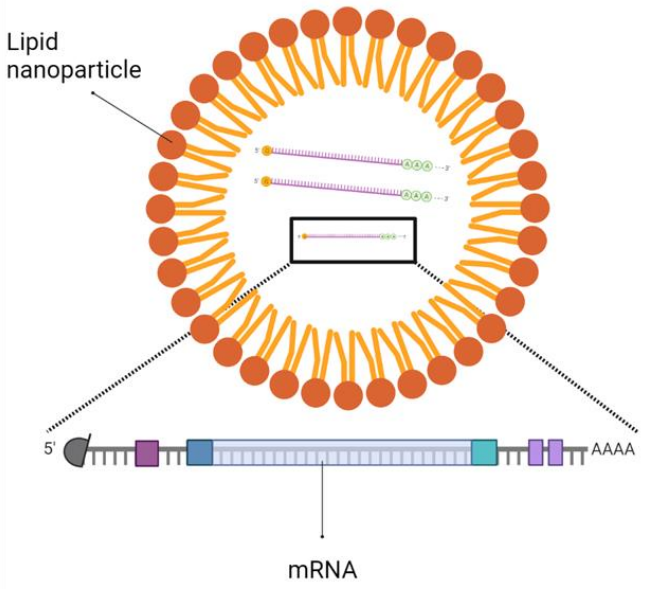

Figure 5: "mRNA-1273" enclosed inside lipid nanoparticle (Created in https://biorender.com/)

Nanoparticles are advance technology and they provide many distinctive advantages that are not present in the conventional methods of the drug delivery systems. These advantages include safer delivery into the host cell, increased surface area and protects the mRNA from degradation. The Moderna Inc Company has used this nanotechnology to speed up the development of their mrna- 1273 vaccine for SARS-cov-2 [24].

6. Route of administration (Intramuscular delivery)

The vaccine should be injected intramuscularly into the deltoid muscle. The reason vaccines are injected intramuscularly is because muscles provide better vascularity which permits the vaccine to reach quickly in systemic circulation and then a powerful adaptive immune response can be generated. This route of administration is more practiced and is an easy to be carried out. Furthermore no special training is required for its administration [25].

7. Doses

The number of doses for the vaccine to properly function are two (Table 3), Necessity of two doses: A week immune response is generated after a few weeks in the people who have received only a single dose while the vaccine was in under testing. It was accompanied by a strong immune response when a second dose was delivered [26].

Table 2: Doses of mrna-1273 [26]

Dose	Strength	Day
1	0.5mL/100mcg	1
2	0.5mL/100mcg	28

8. Composition

The vaccine composing ingredients are listed in (Table 2) [27]

Table 3

Serial number	Constituent	Name
1	Activated mrna	nucleoside-modified messenger RNA encoding the SARS-CoV-2 spike glycoprotein (S) stabilized in its prefusion configuration
2	Lipids	SM-102, polyethylene glycol [PEG] 2000-dimyristoyl glycerol [DMG], cholesterol,and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]
3	Acid stabilizers	Tromethamine & tromethamine hydrochloride
4	Acids	acetic acid
5	Salts	sodium acetate
6	Sugars	sucrose

9. Mode of action

After the administration of the lipid nanoparticle in the recipient, the nanoparticle travels up to the human cell and their it releases the mRNA into the cytsol of the cell. The mRNA migrates to the rough endoplasmic reticulum and there this mRNA is translated into the specific spike protein by utilizing the cells manufacturing tools. This Moderna mRNA 1273 contains the 2P mutation. This spike protein initiates the immune response that leads to the formation of antibodies inside the body. Now if the recipient is ever infected by the SARS-cov-2 in his life later, the antibodies that are produced earlier will recognize the virus and will initiate an immune response that will help into eradicating the virus from the body [18]. A few of the spike proteins produced inside the cytosol are transferred out of the cell and bind with the cell membrane or the proteins can be broken down by the vaccinated cells into small subunits, these fragments are then presented on the surface of the cells. These cells then can be identified by the immune system (Figure 6).

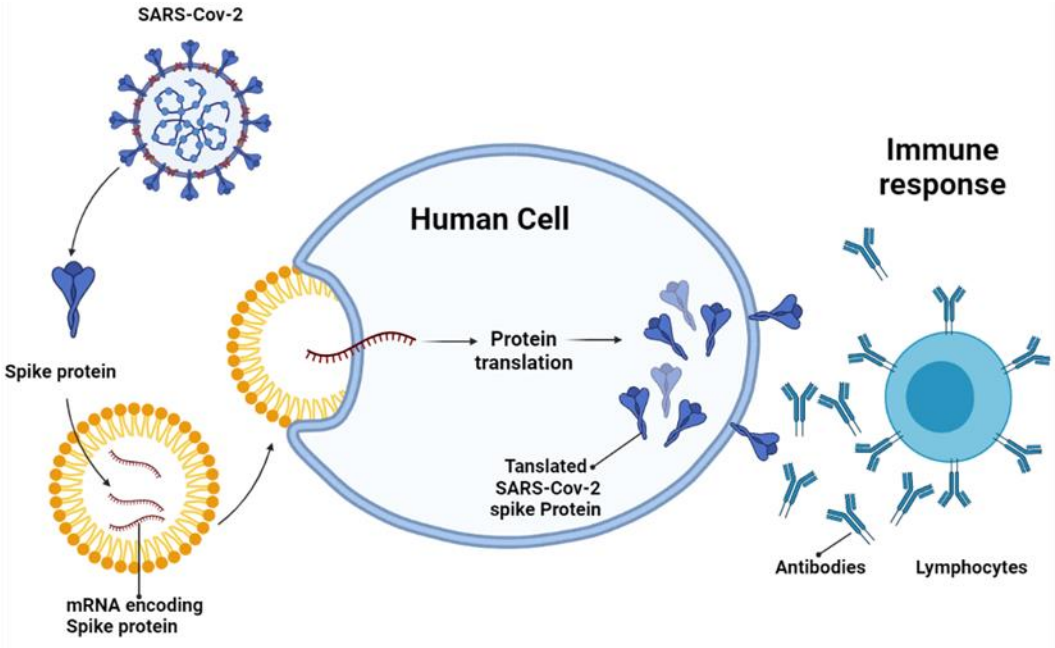

Figure 6: Mode of action of mRNA – 1273 (Created in https://biorender.com/)

10. Immune response

The adaptive immune response is further divided into two parts; cellular or cell mediated immune. The adaptive immunity can be initiated by the help of the following pathways (Figure 7) [28].

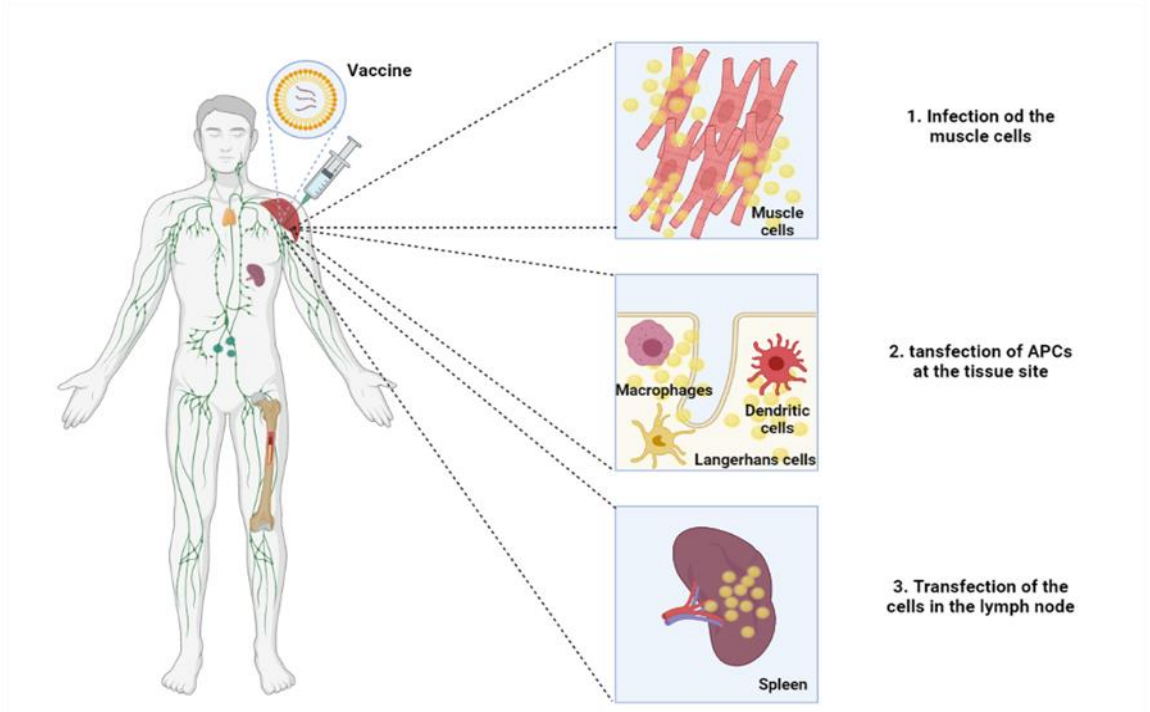

Figure 7: Pathways through which mRNA vaccine can initiate immune response (Created in https://biorender.com/)

1) Infecting the epidermal cells and the myocytes, both are somatic cells.

2) Infecting the immune cells that are residing in the site of injection.

3) Infecting the immune cells present in the lymphoid organs such as the lymph nodes and the spleen.

11. Cellular Immune response

This type of immune response is initiated when the vaccinated non-immune cells break down the spike proteins and form epitopes which then form a complex with MHC class 1 and then these antigens are presented to the CD8 killer T cells. The infection of the muscle cells also leads to the activation of the bone marrow derived dendritic cells which will further lead to the priming of CD8 cells (Figure 8). The transfection in the immune cells, Antigen presenting cells which are mostly dendritic cells and macrophages, present at the tissue site can lead to presentation of the antigen onto MHC class 1 molecules. This results in the maturations of the CD8 T cells. These CD8 cells trigger all the cells that are presenting the antigen to undergo apoptosis [28].

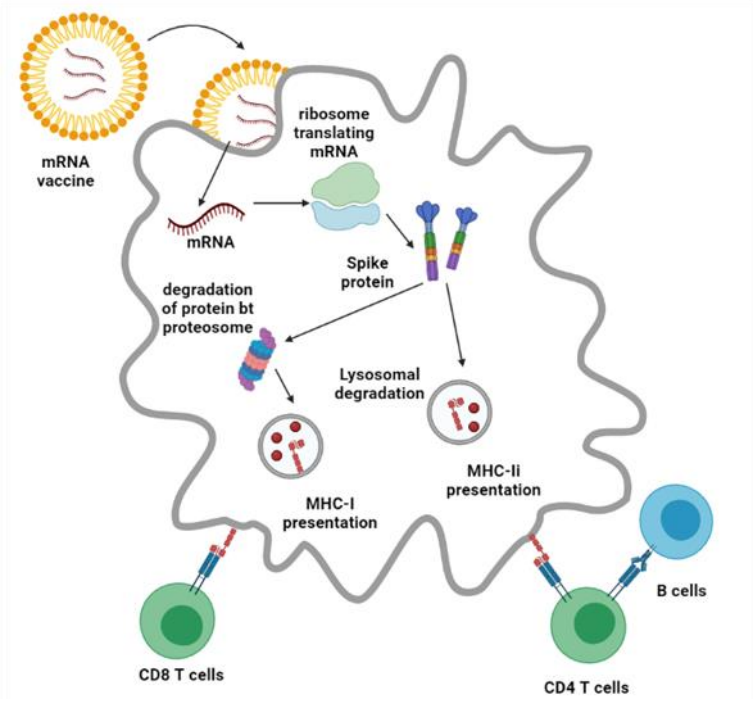

Figure 8: Pathway of initiation of cellular and humoral immune response (Self made) https://biorender.com/

12. Humoral Immune response

Now the transfected antigen presenting cells can also express the antigen through MHC class 2 molecules which results in the activation of the CD4 Helper T cells. The mRNA vaccine can also be drained by lymph into the lymph nodes where it can infect the Antigen presenting cells and endothelial cells residing there. The infection of these cells can lead to the activation of both T and B cells. The activation of the B cells by the CD4 cells or in the lymph nodes leads to the development of the antibodies. The activated B cells further undergo through the

processes in the germinal centers and produce memory B cells. The ultimate goal of the vaccine is to develop these memory cells which can recognize the antigens when the body gets infected by the actual virus [28].

13. Clinical trials

Trials initiated in the Moderna country of origin: The first ever dose of Moderna mRNA-1273 was received by a 43 year old women on 16th March, 2020, during the first clinical trials conducted by the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) and Moderna Inc Company in the Kaiser Permanente Washington Health Research Institute in Seattle, Washington, United States [29].

14. Phases

The first clinical trial involved a total of 120 adults who were 18 to 99 years of age. This trial was dose dependent, three different doses of mRNA 1273 were given. Minor symptoms like headache, fatigue, chills and fever were observed. This study showed adequate amount of immune response is generated in volunteers. The second phase of the clinical trial involved 660 adults who were 18 years or older. The study was divided into three parts. In Part A volunteers either received the vaccine or a placebo. In Part B volunteers where given the choice to request the dose of vaccine if they were given a placebo in part A or a single booster if they received the vaccine in part A. Part C was carried out to study the efficacy of vaccine for mutations. The third phase of the clinical trial involves 30420 participants who are 18 years or older. This study was divided into two parts. In part a participants either received the active mRNA vaccine or the placebo. In part B the participants who received placebo in part A could request for the vaccine. The 3rd phase showed an efficacy of 94.5% [22].

15. FDA approval

Moderna COVID-19 Vaccine was approved on 18th December, 2020 to be utilized under an Emergency Use Authorization (EUA) for active immunization against the covid 19 disease and this vaccine is investigational and is not approved by FDA yet. (Moderna), (FDA)

16. Efficacy

The mRNA 1273 vaccine showed an efficacy of 94.1 percent in the people who are 18 years older and are never infected by the virus after receiving two doses of the vaccine. This vaccine is equally effective among the people irrespective of their age, gender, race and geographical regions, which is proved in the clinical trials [30].

17. Efficacy of Moderna-1273 for different variants of SARS-Cov-2

Moderna has released a new study which shows that the mRNA vaccine is proficient enough to develop antibodies against all variants including alpha, gamma, beta, delta, epsilon and lota. A majority of the participants involved in this study showed the presence of detectable amount of antibodies after 6 months. The efficacy of the vaccine is same for all the variants [18].

18. Comparison of different vaccines for covid 19

Table 4: Comparison of different vaccines for covid 19 [31]

	Moderna	**Pfizer**	**AstraZeneca**	**Novavax**	**Johnson & Johnson**
Types of vaccine	mRNA	mRNA	Inactivated common cold virus	Recombinant protein	Vector based
Doses	2, 28 days apart	2, 21 days apart	2, 4-12 weeks apart	2, 21 days apart	1
Approval date	18th December, 2020	11th December, 2020	28th January, 2021	*	27th February, 2021
Age limit	18 years or older	12 years or older	18 years or older	18 years or older	18 years or older
Effective against hospitalization	Yes	Yes	Yes	Yes	Yes
Effective against death	Yes	Yes	Yes	Yes	Yes
Efficacy	94.1%	95%	70%	89.6%	72%

19. Conclusion

The Moderna mRNA-1273 vaccine is developed by using the latest nanotechnology. The trials and studies show that the mRNA based vaccine has a higher efficacy as compared to the other developed by conventional methods. The reason of the success of mRNA-1273 is its rapid and economic development. It takes less time to develop the vaccine so it is more helpful in case of deadly emerging viruses. It contains no activated particle that can cause severe illness in the recipient. The most promising advantage of mRNA-1273 is that it does not enters in the nucleus of the cell. The mRNA remains inside the cytosol and hence there are no chances of insertional mutagenesis. This vaccine is also effective against the present variants of covid 19.

20. Recommendations

According to the recorded fact and figures, mRNA based vaccines are exhibiting the promising results and it is also paving the paths for the scientists to use this technology for preventing and treating the other contagious and lethal diseases.

Conflict of Interest

All the authors don't have any conflict of interest regarding this manuscript.

References

[1]. Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., ... & Yan, Y. (2020).The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Military Medical Research. 2020; 7: 11. doi. org/10.1186/s40779-020-00240-0.

[2]. Haleem, A., Javaid, M., & Vaishya, R. (2020). Effects of COVID-19 pandemic in daily life. Current medicine research and practice, 10(2), 78.

[3]. Hussain, M., Jabeen, N., Raza, F., Shabbir, S., Baig, A. A., Amanullah, A., & Aziz, B. (2020). Structural variations in human ACE2 may influence its binding with SARS-CoV- 2 spike protein. Journal of medical virology, 92(9), 1580-1586.

[4]. Zumla, A., Chan, J. F., Azhar, E. I., Hui, D. S., & Yuen, K. Y. (2016). Coronaviruses— drug discovery and therapeutic options. Nature reviews Drug discovery, 15(5), 327-347.

[5]. Tang, C. Y., Wang, Y., Gao, C., Smith, D. R., McElroy, J. A., Li, T., ... & Wan, X. F. (2021). Increased SAR-CoV-2 shedding associated with reduced disease severity despite continually emerging genetic variants. medRxiv.

[6]. Chadha, J., Khullar, L., & Mittal, N. (2021). Facing the wrath of enigmatic mutations: A review on the emergence of SARS-CoV-2 variants amid COVID-19 pandemic. Environmental microbiology.

[7]. Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug discoveries & therapeutics, 14(1), 58-60.

[8]. Prompetchara, E., Ketloy, C., & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific journal of allergy and immunology, 38(1), 1-9.

[9]. Porter, K. R., & Raviprakash, K. (2016). DNA vaccine delivery and improved immunogenicity. Current issues in molecular biology, 22(1), 129-138.

[10]. Lazo, L., Valdes, I., Guillén, G., Hermida, L., & Gil, L. (2019). Aiming at the heart: The capsid protein of dengue virus as a vaccine candidate. Expert review of vaccines, 18(2), 161-173.

[11]. Iavarone, C., O'hagan, D. T., Yu, D., Delahaye, N. F., & Ulmer, J. B. (2017). Mechanism of action of mRNA-based vaccines. Expert review of vaccines, 16(9), 871-881.

[12]. Funk, C. D., Laferrière, C., & Ardakani, A. (2021). Target product profile analysis of COVID-19 vaccines in phase III clinical trials and beyond: an early 2021 perspective. Viruses, 13(3), 418.

[13]. Verch, T., Trausch, J. J., & Shank-Retzlaff, M. (2018). Principles of vaccine potency assays. Bioanalysis, 10(3), 163-180.

[14]. Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines—a new era in vaccinology. Nature reviews Drug discovery, 17(4), 261-279.

[15]. Jackson, N. A., Kester, K. E., Casimiro, D., Gurunathan, S., & DeRosa, F. (2020). The promise of mRNA vaccines: a biotech and industrial perspective. npj Vaccines, 5(1), 1-6.

[16]. Schlake, T., Thess, A., Fotin-Mleczek, M., & Kallen, K. J. (2012). Developing mRNA- vaccine

technologies. RNA biology, 9(11), 1319-1330.

[17]. Verbeke, R., Lentacker, I., De Smedt, S. C., & Dewitte, H. (2021). The dawn of mRNA vaccines: The COVID-19 case. Journal of Controlled Release, 333, 511-520.

[18]. Moderna (2021). About Moderna Inc company. Company history and information: MRNA science. Retrieved from https://www.modernatx.com/about-us/moderna-facts

[19]. Nasdaq (2021). Financial reports for Moderna Inc from 2017 to 2020. Retrieved from https://www.nasdaq.com/market-activity/stocks/mrna/financials

[20]. Nobanee, H. Financial Analysis and Performance Evaluation of Moderna.https://www.researchgate.net/profile/Haitham,Nobanee/publication/353571480_Financial_Analysis_and_Performance_Evaluation_of_Moderna/links/6103a9c91ca20f6f86ea31f6/Financial-Analysis-and-Performance- Evaluation-of-Moderna.pdf

[21]. Banerjee, A. K., Begum, F., & Ray, U. (2020). Mutation hot spots in Spike protein of COVID-19. Preprints, 2020, 2020040281.

[22]. Teo, S. P. (2021). Review of COVID-19 mRNA Vaccines: BNT162b2 and mRNA- 1273. Journal of Pharmacy Practice, 08971900211009650.

[23]. Buschmann, M. D., Carrasco, M. J., Alishetty, S., Paige, M., Alameh, M. G., & Weissman, D. (2021). Nanomaterial delivery systems for mRNA vaccines. Vaccines, 9(1), 65.

[24]. Khurana, A., Allawadhi, P., Khurana, I., Allwadhi, S., Weiskirchen, R., Banothu, A. K., ... & Bharani, K. K. (2021). Role of nanotechnology behind the success of mRNA vaccines for COVID-19. Nano Today, 38, 101142.

[25]. Reichmuth, A. M., Oberli, M. A., Jaklenec, A., Langer, R., & Blankschtein, D. (2016). mRNA vaccine delivery using lipid nanoparticles. Therapeutic delivery, 7(5), 319-334.

[26]. Livingston, E. H. (2021). Necessity of 2 doses of the Pfizer and Moderna COVID-19 vaccines. JAMA, 325(9), 898-898.

[27]. Kisby, T., Yilmazer, A., & Kostarelos, K. (2021). Reasons for success and lessons learnt from nanoscale vaccines against COVID-19. Nature Nanotechnology, 1-8.

[28]. Kim, J., Eygeris, Y., Gupta, M., & Sahay, G. (2021). Self-assembled mRNA vaccines. Advanced Drug Delivery Reviews.

[29]. Wang, F., Kream, R. M., & Stefano, G. B. (2020). An evidence based perspective on mRNA-SARS-CoV-2 vaccine development. Medical science monitor: international medical journal of experimental and clinical research, 26, e924700-1.

[30]. CDC (2021). Moderna COVID-19 Vaccine Overview and Safety. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Moderna.html Moderna (2021). About Moderna Inc company. Company history and information: MRNA science. Retrieved from https://www.modernatx.com/about-us/moderna-facts

[31]. Siddique, S., & Ahmed, S. (2021). COVID-19 Vaccines in Pakistan: Efficacy, Adverse Effects and Availability. Journal of Islamabad Medical & Dental College, 10(2), 125-130.