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A Systematic Overview on SARS CoV-2 Pandemic & Pfizer-BioNTech COVID-19 Vaccine

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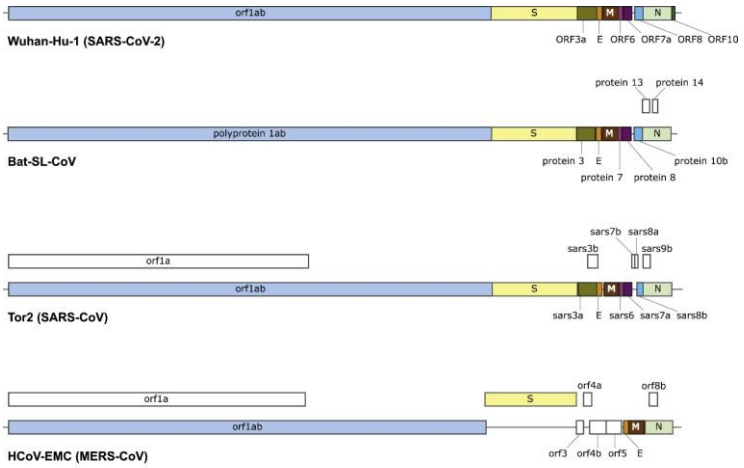
Abstract:- SARS-CoV-2 originated in Wuhan, Hubei province of China and was declared as a pandemic by WHO in March 2020. It has not been the first time this world has been hit by a lethal pandemic. Spanish Flu prevailed a century back whereas SARS-CoV-1 and MERS like viruses have also ensnared in the form of epidemics. Such lethal viruses establish themselves in the human population by aquiring the mutations and resultantly enhance their pathogenicity. Up till now many variants of SARS-CoV-2 has been reported, one of the biggest reasons is the briskly aquiring mutations rate as it is a single stranded RNA virus that lacks proof reading ability. Currently, delta variant is spreading with the greatest mortality rate. Ever since China has released the genomic sequence of SARS-CoV-2 online, researchers from all over the world have joined hands to come up with a vaccine. More than 90 vaccines have underway but only a few have been approved by FDA for administration into human beings. Emergency Use Authorization has been granted to a lot of vaccines and Pfizer is the first mRNA vaccine to have succeeded all the trials with an efficacy of more than 90 % against Covid-19. In this review, short briefing is provided related to all the important vaccines worldwide while a detailed review of PfizerNBiotech has been given to highlight the prospects of a vaccine which is new in its kind.

Keywords:- *Covid-19; Vaccines; PfizerBioNtech; immune responses; Doses; Efficacy; Variants; mRNA based vaccines; clinical trials.*

I. BRIEF HISTORY OF PANDEMICS

Covid-19 also known as SARS-CoV-2 has evolved indirectly or directly from the beta coronavirus in sarbecovirus (viruses similar to SARS). This particular group causes infections in pangolins and bats belonging to Southeast Asia and Asia [1]. A lot of scientists had already predicted the emergence of SARS viruses, time and time again in their articles or on social media platforms. SARS-CoV-1 was responsible for causing a pandemic in 2002-2003 [2]. In 2012, MERS (Middle East Respiratory Syndrome) emerged which also belonged to β-Coronaviruses. In 2016, alpha Coronavirus prevailed in the Chinese population and as it was transmitted from consumptions of swines, it was termed as swine acute diarrhea syndrome coronavirus (SADS-CoV).The worst pandemic was in 1919 when Spanish Flu killed more than 50 million people across the globe [3]. Sequence homology exist between these above mentioned SARS-CoV-1, SARS-CoV-2 and MERS (Fig 1) However, before 2019 no genetic sequences related to SARS-CoV-2 had been identified early among humans or animals**.**

Species of bats have a great reservoir of coronaviruses. SARS-CoV-1, MERS and Covid-19 all belong to β lineage of coronaviridae family that give rise to two phylogenetic sub classes of Sarbecoviruses (SARS-like virus) and merbecovirus (MERS-CoV like virus). SADS, SARS-CoV-1 and SARS-CoV-2 all descend from horse shoe bats specifically [4].



	orf1ab	S	ORF3a	E	M	ORF6	ORF7a	ORF8	N	ORF10
SARS-CoV-2										
Bat-SL-CoV	95%	80%	91%	100%	98%	93%	88%	94%	94%	-
SARS-CoV	86%	76%	72%	94%	90%	68%	85%	40%	90%	-
MERS-CoV	50%	35%	-	36%	42%	-		-	48%	-

Figure 1: Comparative analysis of the genome structures of SARS-CoV-2 with Bat Relative [bat-SL-CoVZXC21], [Tor2 SARS-CoV], and [HCoV-EMC MERS-CoV] [5]. Above: Coding sequence (CDS) regions with the homology are filled with same color boxes while the regions with no homology with the SARS-CoV-2 proteins are colored with white.

II. HOW DO VIRUSES ESTABLISH THEMSELVES IN THE HUMAN POPULATION?

Viruses are basically nucleic acids associated with proteins or sometimes lipids. They can basically of two types; RNA or DNA viruses. Viruses are obligate intracellular parasites that will only replicate once inside the host cell. Viruses utilize the host cell machinery to make their own proteins and make progeny [3]. It usually happens that a virus

enters the human population through some other host for instance an insect or animal. This is referred as host switching when the virus leaves its primary host and establishes itself in a secondary host to complete the viral replication cycle. Many of non-viral and viral infections i.e HIV, measles, chicken pox, cholera, malaria, dengue, influenza etc have spread from switching of hosts. Certain genetic changes occur that cause a virus to propagate in an entirely different set of population [6]. These genetic mutations are owing to a change in social, biological or environmental factors. Such changes provide perfect opportunity for a virus interact with other species, create quasispecies of its own, evolve cell receptors and acquire ability to cause pathogenesis in another host with a different set of conditions [7].

The reason SARS-CoV-1 and Covid-19 emerged from Huanan live sea food market in China is because the country is home to more than 100 species of bats which are carriers of both α and β Coronaviruses. There are more than 31 species that are reservoirs of β-type coronaviruses alone. SARS-CoV and SARS-CoV-2 emerged in China, home to bats of more than 100 species, many of which carry α- and/or β-coronaviruses [7]. In one study, more than 780 partial coronavirus genetic sequences were identified from bats of 41 species infected by α- and of 31 species infected by β-coronaviruses. RNA-dependent RNA polymerase from Bat-CoV-RatG13 (bat coronavirus) showed 96% similarity to SARS-CoV-2. This close phylogenetic relation with RaTG13 provided evidence to the world that Covid-19 can be traced back to bats [8]. SARS-CoV- 2 have emerged through a series of natural selection process from the β-Coronavirus family. There is significant similarity with other six members of the same family. However, Covid-19 manifested a new trend of zoonosis in which there has been a "host jump" directly from a primary host (bats) to the secondary (humans) without any intermediary host (Fig 2). Scientists have reported an insertion of four amino acids into the genome's structure. It is through this additional sequence; the virus has acquired ability to replicate in human cells [9].

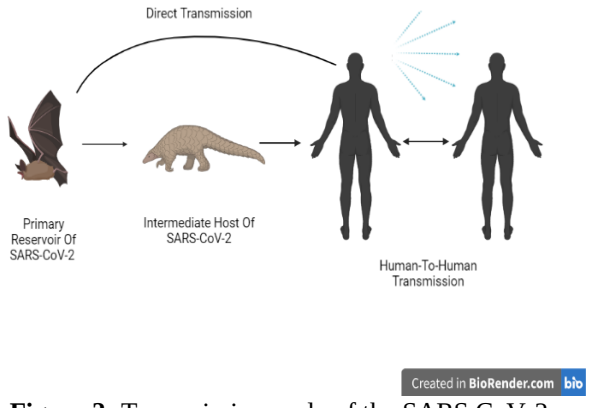


Figure 2: Transmission cycle of the SARS CoV-2

III. SARS-COV-2 AND ITS VARIANTS

To this date, four variants of Covid-19 have emerged and spread like wild fire in all parts of the world. The Alpha Strain- B.1.1.7 was first identified in United Kingdom in December 2020. The Beta Strain B.1.351 was first isolated in South Africa. The Gamma Strain- P.1 was identified in Brazil and Japan in 2021. Currently, the world is going through the delta wave- B.1.617.2 strain which belongs to India and has the highest fatality rate so far (CDC, 2021).

Covid-19 has accumulated a lot of mutations in its genome especially in its Spike protein. The more the mutations, the more virus is able to infect and complete its pathogenesis. Covid-19 is a single-stranded RNA enveloped virus that binds to host cells via its spike protein (S) [10]. The S protein has two subunits S1 and S2; a receptor binding domain (RBD) which is present on S1 plays the most important role in facilitating viral entry followed by infection. This RBD has the greatest affinity for human-angiotensin-converting-enzyme-2 (ACE-2) [11]. RNA viruses have a great tendency for accommodating mutations in their sequences as they lack proof reading ability. Thereby, their virulence and evolution are far greater than DNA viruses. Similarly, SARS-CoV-2 has undergone a lot of changes and continues to evolve to this date. Most of the mutational clusters are located in the RBD of S1-subunit. To this date, about 1800 mutations have been reported in Spike protein. About 235 mutations have accumulated in receptor binding domain (RBD). The virus is continuously evolving to increase its pathogenicity and become resistant to viral drugs [12].

Genetic analysis have proven that since the original SARS-CoV-2 outbreak in Wuhan, many lineages or clades have emerged ever since then. They have been classified into A1a, A2, A2a, A3, A6, A7, B, B1, B2, B4 and O [10]. The most common mutations of S-protein have been categorized into A2, A1a and A2a lineages. The virus keeps undergoing positive selection and now possesses many transmissible clades. The majority of the mutations are deletion, insertion and replacement of amino acid sequences. Mutations at V367F, D364Y, N354D and W436R have significantly increased the affinity to ACE-2 receptors in humans. Samples of North America highlighted two hot spots V483A and G476S in the Ribosome binding domain of S protein [13]. Evolving of mutations occur due to immune responses as well as drug exposure. That is why RNA viruses are capable of crossing the species barrier and adapting to a new host for completion of replication cycle. 100,000 copies as present per ml of an infected person's saliva which indicates a high viral titre in human body [14]. All the above-mentioned characteristics make Covid-19 at a great risk of antigenic drift and accumulate immunologically acquired mutations in various ethnic groups [13]. If mutations in the interface region of ACE2-RBD are acquired (Fig 3), infectivity rate will be enhanced manyfold [15].

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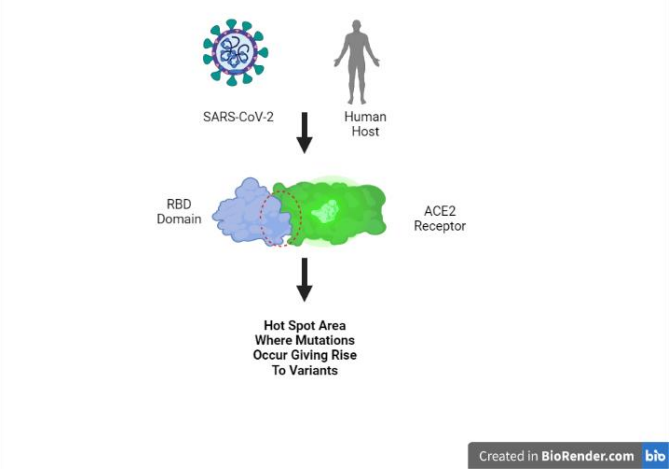

Figure 3: Mutational hotspots for the generation of variants

IV. VACCINES SO FAR

It has been observed that spike protein alterations like N501Y mutation enhance the transmission capability of the virus. This N501Y mutation is part of virus that attaches to human cell receptor ACE2. It is one of the hit points for vaccine development. E484K, is another mutation which affects spike protein's receptor binding domain in variant 501Y.V2. This is another target for vaccines to hit [16].There are various types of vaccines that are being developed against SARS-CoV-2. These include inactivated vaccines, viral vector replicating and non-replicating vaccines, conjugate, toxoid, nucleic acid-RNA based vaccines, protein sub-unit vaccines and the most recent of all mrna based vaccines. To this date about 90 vaccines are in progress in various research institutes all over the world [17].

Covid-19 emergence set all researchers to develop vaccines against this virus. For the first time in history, an mrna vaccine has been developed and so far, it is the most successful with respect to efficiency and providing protection against variants. Moderna is an mrna based vaccine developed in United States of America. It is delivered via lipid nanoparticle and has instructions related to spike protein of coronavirus [18]. These specific genetic instructions guide cells to make proteins in human body. The first prototype was designed in January, 2020 and it gained a physical form in just about three months. On November 2020, it was approved by FDA and authorization was granted in December. To this date, it is being administered to patients [19].

CanSino is a non-replicating viral vector type vaccine which utilizes adenovirus type 5 vector for delivering the DNA sequence of spike protein. It was the first Chinese vaccine to begin its human trials. However, its third phase trails had some obstacles before it was cleared for administration. It has a efficiency of about 65% against SARS-CoV-2 [19]. The vaccine is being modified into an inhaled version. Booster shots are also being developed. However, there are several reports that claim CanSino's method of delivery is compromising its method of effectiveness [20]. Sinovac is an inactivated type viral vaccine in which SARS-CoV-2 is weakened via chemical treatment. This vaccine has been largely administered in Pakistan. China is currently manufacturing millions of Sinovac doses and supplying those 26 countries. It is also an FDA approved vaccine. It has an efficacy of about 83.5% in symptomatic cases [21].

Sinopharm is being manufactured by Beijing Institute in China. The virus has been inactivated by chemical treatment in this vaccine. It has about 79% efficacy. It is also an FDA approved vaccine that is currently being supplied to more than 30 countries. Its trails reported no complications [22].

AstraZeneca is yet another FDA approved vaccine but worldwide its adverse effects have gained attention. That is why it is only recommended to a limited age group. It's a non-replicating viral vector vaccine in which DNA sequence for spike protein is delivered via viral vector of chimpanzee. It is being manufactured in United Kingdom by Oxford University. The best advantage of Astra Zeneca is its storage conditions which are easy to meet. Also, it is cheaper than the rest of the vaccines [23].

Novavax is the first protein-based vaccine against SARS-CoV-2. Its working mechanism includes the production of coronavirus derived protein in cell lines of insects. These proteins are extracted and then delivered along with an adjuvant. Its trial results showed an efficacy of about 90%. However, the vaccine is facing certain set-backs in its production process and hence its international delivery [24].

BioNTech Pfizer is a vaccine developed by Germany and America. It's a mrna based vaccine in which genetic instructions for spike protein encoded in mrna are delivered through lipid nanoparticles [25]. To this date, Pfizer remains the most promising vaccine. It has more than 95% efficacy against Covid-19. A study in UK proves that Pfizer is the only vaccine effective against the delta strain as well. It offers 88% protection against the rapidly mutating delta strain. Comparison of some widely used vaccines are mentioned in (Table 1)

V. FORMULATION OF BIONTECH PFIZER

Pfizer is a German Company who partnered with the American company Pfizer to develop the first m-Rna corona vaccine. The vaccine was called as BNT162b2. Its generic name is tozinameran with the brand name Comirnaty. It takes about 60 days to produce one batch of Pfizer vaccine. Each vaccine vial has about five doses of 0.3 milliliters [27]. Before the injection can be administered, the vial must be thawed and diluted with saline. Once the dilution step has taken place, the vaccine must be consumed within 6 hours. Above freezing temperatures, the vaccine will lose all its viability within 5 days [28]. Like many other vaccines, Pfizer also targets the spike proteins present on the surface of Coronavirus. The mRNA molecular containing instructions for the production of covid-19 spike proteins into the human body is wrapped in lipid nanoparticles, otherwise it would be degraded by our natural enzymes [29]. These m-Rna molecules are degraded at room temperature. To ensure sustainability of such a vaccine, PfizerNBiotech have developed specific containers containing dry ice, thermal

sensors as well as GPS trackers so that vaccines can be transported at -70°C to retain its viability, formation process is depicted in the (Fig 4, 5), [30].

Table 1. Comparison of Covid-19 Vaccines

	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, 2-12 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%

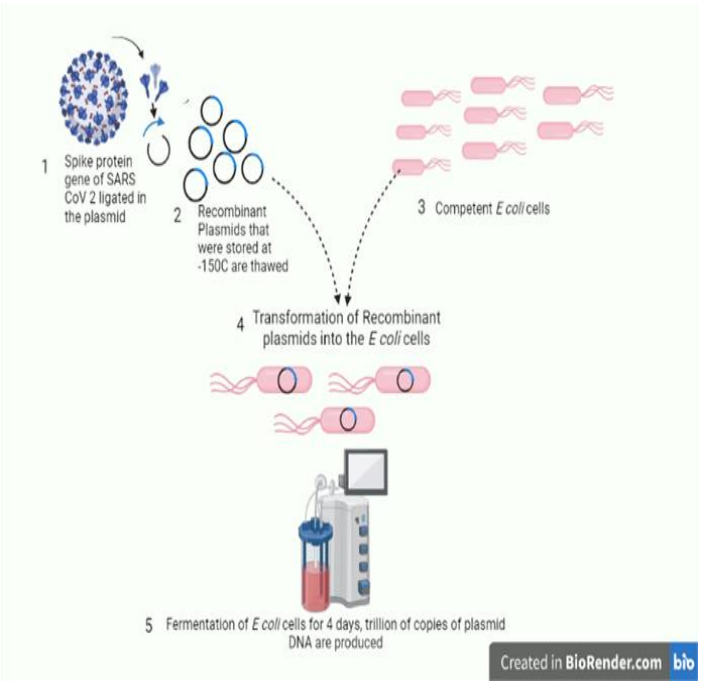

Figure 4: Formation of Pfizer vaccine (Step 1 to 5)

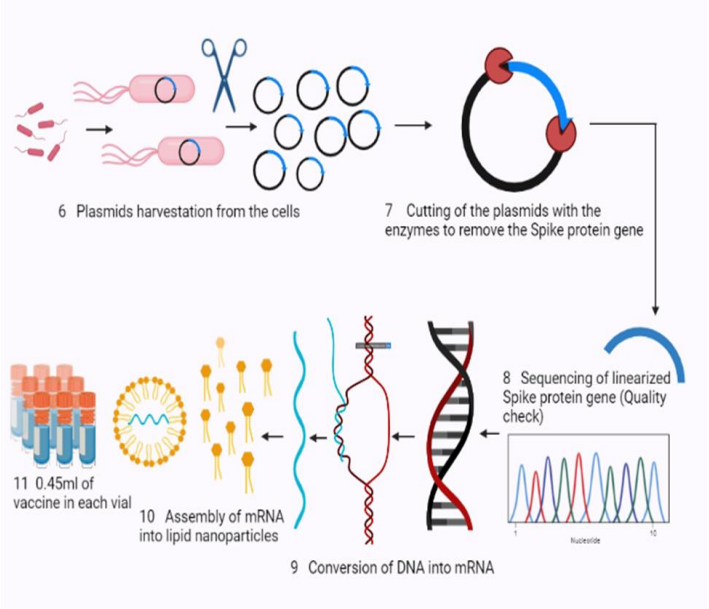

Figure 5: Formation of pfizer vaccine (step 6 to 10)

VI. APPROVAL AND CLINICAL TRIALS OF PFIZER VACCINE

On 2nd December, 2020 United Kingdom approved BNT162 for vaccinations. On 11th December, FDA approved the vaccine claiming it had 95% efficacy [31]. Canada and Mexico also approved Pfizer for Emergency Use Authorization (EUA). On 31st december, WHO approved it is as first vaccine candidate for emergency purposes and granted it permission for mass production [32]. In the initial stage, there were four candidate vaccines of Pfizer. Two were nucleoside modified mRNA (mod mRNA), one had uridine in its mRNA (uRNA), the third was self-amplifying mRNA (saRNA) and the fourth was BNT162b2. In the pre-clinal trial, BNT162b2 and modRNA manifested antiviral effects in Rhesus macaques with a high antibody titre. The same response was observed in mice. These two were shortlisted for trails of phase two and three [33]. On 9th November, 2020 phase 3 trails results were revealed in which BNT162b2 depicted an efficacy of more than 90% against Covid-19 after injecting its second dose. BNT162b2 was preferred over BNT162b1 as its results showed lesser systemic response [34]. Immunogenicity, adverse effects, risks, and contraindications of Pfizer is mentioned in the (Table 2). Frequency of comparative adverse effects of Pfizer/BionTech and moderna is shown in the (Fig 6).

Table 2. [28]

Immunogenicity	Immunogenicity persisted over a median of 2 months
Adverse events	Pain, swelling, redness, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain, lymphadenopathy, shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, syncope, and right leg paresthesia
Anaphylaxis reaction	CDC has identified 6 case of anaphylaxis reaction following Pfizer-BioNTech vaccine
Risks in pregnancy, infant and children	Not Known: the prevention of COVID-19 is not addressed in younger adolescents, children and pregnant women
Contraindication	Individuals with a known history of severe allergic reactions, including anaphylaxis, immunocompromised persons, and individuals receiving immunosuppressive therapy

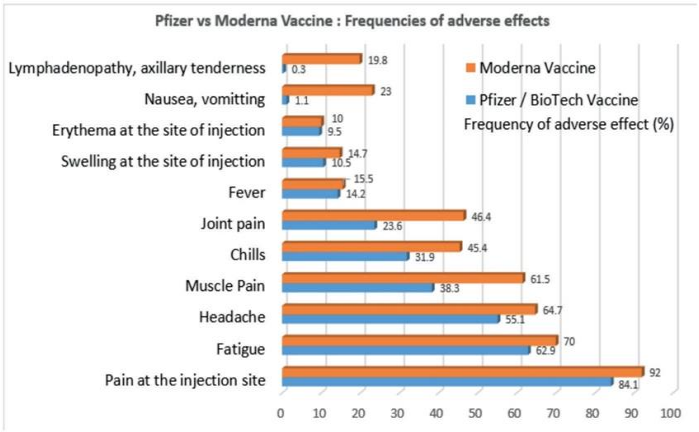

Figure 6: Comparison between frequencies of adverse effects of Pfizer/BioNTech and Moderna Vaccines [28]

VII. MODE OF ACTION AND IMMUNE RESPONSES OF PFIZER VACCINATION

Research on therapeutic mRNA has been going on for decades. It was in 1990 that the first mRNA molecule was injected into mice. However, a strong inflammatory response degraded the mRNA molecule and scientists were not able to move ahead with the experiment. It was recognized by Weissman and Kariko that our immune cells recognized mRNA as a foreign particle and degraded it completely [29]. It was after a decade later that they figured out a way of masking this mRNA molecule as a normal cell with the help of a modified nucleotide. This allowed entry of mRNA molecule into the cell without triggering any inflammatory response. They tested more than 40 delivery systems and landed on lipid nanoparticles which were not only protected the mRNA but also ensured its specificity of targeting a particular cell. These lipid molecules also acted as an adjuvant in stimulating an immune response in the host that promoted antibody production [35].

SARS-CoV-2 vaccine was synthesized keeping a similar principle in mind. Once the injection has been administered, the particles of vaccines fuse with the host cells and un-coat to release their mRNA molecule. Our body cells are capable of reading the sequence inside these molecules and follow instructions to produce Covid-19 spike proteins. Viral proteins are made inside the muscle cells and reach a peak within 24 to 48 hours [36]. The initial mRNA molecule eventually diminishes as it is destroyed by our immune cells so that no trace is left behind. Some of the formed spike proteins migrate to the cell's surface and manifest their tips on top of the cell. Certain proteins are also fragmented and later expressed on the surface of the host cell. These spike proteins and their fragments can be recognized by our body's immune system. When any vaccinated cell dies, the debris of such cells contains a lot of SARS-CoV-2 spike proteins and fragments that are engulfed by our immune cells, forming an Antigen Presenting Cell [37]. The Helper T cells, recognize these fragments or spike proteins and release signals that guide other immune cells to fight off the infection. B cells spring into action and come in contact with many spike proteins on the surface of vaccinated cells or fragmented spike proteins. Once a B cell has locked itself on the spike protein or a small fragment, it will proceed towards antibody production. The antibodies serve the purpose of attaching to other spike proteins and mark them for destruction. These immunoglobulins prevent the spread of infection by blocking attachment sites on the spike protein so that no attachment can occur with the host cells. The antigen presenting cells not only activate B cells but are responsible for activating other cells of the immune cells including killer T cells. These cells are on the hunt for cells infected with the virus or cells that are expressing spike proteins of Covid-19 [38]. Mode of action and immune responses are shown in the (Fig 7).

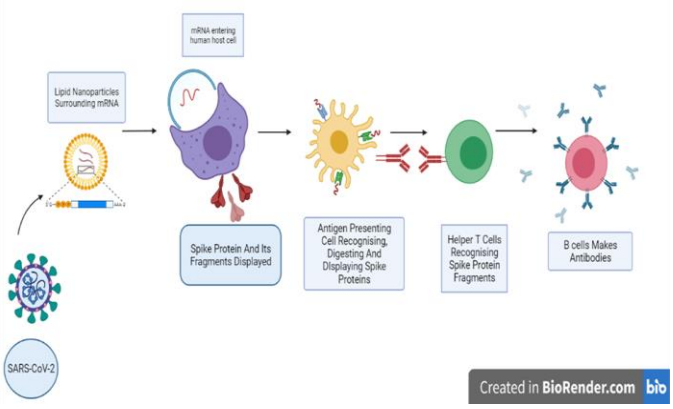

Figure 7: Mode of action and immune responses

Pfizer-BioNTech is administered in two doses. The second dose is injected after 21 days of the initial dose. Since this is the first mRNA vaccine to be commercialized so soon, no one knows the time span for which it will offer protection.

Preliminary data revealed that the vaccine was capable of offering protecting after 10 days of the first dose [39]. It must be considered that the number of B and T cells will decline after a few months. Scientists are hoping that memory T and memory B cells will retain the instructions given by mRNA molecule so that a lifetime immunity is established within human bodies [40].

VIII. EFFECTIVENESS OF PFIZER VACCINE FOR EMERGING VARIANTS

As the new variants of SARS CoV-2 are emerging by the time, so the vaccines must also have the effectiveness against these novel variants. These new variants are mostly having the mutations in the Spike protein gene region, so that's why the Pfizer and BioNTech are working on formulating the new versions of Pfizer vaccine, in order to make it effective against these new variants. For that purpose the scientists are changing the Spike protein gene according to the new aquired mutation [41]. It has been depicted in the (Fig 8).

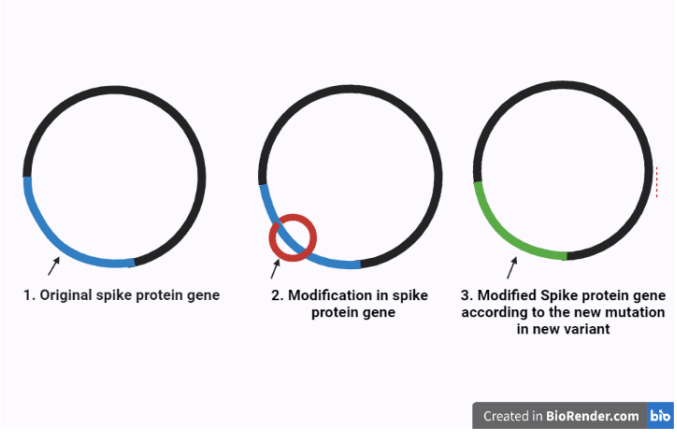

Figure 8: Modification of spike protein gene in order to make the effective Pfizer vaccine against newly emerged SARS CoV-2 variants

IX. THE MRNA MIRACLE

Vaccines are developed to train our immune system to recognize an infection causing part of a viral antigen. Traditionally vaccines contain weakened viruses or purified form of viral proteins. mRNA and its working mechanism is quite different because it involves a person receiving the most basic genetic instructions to recreate viral proteins [42]. When this mRNA molecule is injected into the muscles of upper arm, the muscle cells begin translating the mRNA molecule to generate viral proteins in the human body [43].

The best vaccines are those that mimic natural pathway of the virus. That is why an mRNA vaccine is a promising and so far, the best vaccine to be commercialized in market. The mRNA molecular does not code for the entire spike protein but a critical portion of the surface protein which is capable of causing infection [44].

The traditional methods of developing vaccines are not only complex but also very time consuming. They are also incapable of responding simultaneously against SARS-CoV-2 antigens. For instance, it takes about six months for the flu viral particles to be identified, isolated and regrown in the form of a hybrid virus which is grown inside eggs of hen. The injected eggs are incubated so that number of copies are enhanced. The viral proteins are extracted and purified several days later [45].The mRNA vaccines have no such lengthy protocols to abide by. It just provides the set of instructions to the body at a molecular level and the rest of the job is done by our own body cells. It must also be considered that mRNA molecules are much simpler as compared to proteins. This mRNA is artificially synthesized in labs so there is no need for using biological methods for growing a molecule or virus and then isolating it. Days after the genetic sequence was revealed by China, mRNA code for the virus and its proteins was ready. Once the scientists have fully understood to make an mRNA vaccine, it will be put into use for future pandemics as well [46].

X. SETBACKS OF AN MRNA VACCINE

Though the mRNA technology is not new. It has been experimented on animals that whenever an mRNA molecule containing a set of instructions is injected, the cells are capable of producing the desired proteins. mRNA vaccines have been studied for Zika virus, rabies, flu and cytomegalovirus [47]. However, the progress of this methodology was quite slow. That was due to the fact that mRNA is a very fragile molecule that is prone to degradation at all times. It can also be easily eradicated by our human body cells. Therefore, a lifelong protection cannot be ensured by this molecule [48]. Also, the delivery methods of mRNA molecule remain inefficient. It was in 2005 that researchers tapped onto a way of making these molecules stable. However, those methods were not FDA approved and it is only during this pandemic that the process has speeded up and this particular method has gained recognition [49].

The biggest challenge is the preservation of an mRNA vaccine. Any slight changes in temperature can result in the degradation of this molecule. Hence why, modification strategies are being applied to prolong the shelf life of such vaccines. In the meantime, Pfizer is making shipments in containers packaged with dry ice [50].

XI. CONCLUSION

The dawn of mRNA vaccines have provided us a solution to a lethal disease but questions are being raised all over the scientific global community related to its long-term effects. It was the need of the hour to administer this preventive medicine but a lot more study needs to be conducted on children, adults and elder people. Post market surveillance should be carried out to learn about any post administration symptoms. The pregnant ladies and people with comorbidities i.e heart conditions, liver diseases, diabetes and pulmonary hyper tension must be closely monitored to observe any adverse side effects. SARS-CoV-2 seems to have opened up new avenues for vaccine development and if it retains its success, many more viral infections can hopefully be tackled too via mRNA vaccinations.

Conflict of interest

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

REFERENCES

[1]. Morens, D. M., Breman, J. G., Calisher, C. H., Doherty, P. C., Hahn, B. H., Keusch, G. T., ... & Taubenberger15, J. K. (2020). Perspective Piece.
[2]. Cheng, V. C., Lau, S. K., Woo, P. C., & Yuen, K. Y. (2007). Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clinical microbiology reviews, 20(4), 660-694.
[3]. Geoghegan, J. L., & Holmes, E. C. (2018). Evolutionary virology at 40. Genetics, 210(4), 1151-1162.
[4]. Anthony, S. J., Johnson, C. K., Greig, D. J., Kramer, S., Che, X., Wells, H., ... & Goldstein, T. (2017). Global patterns in coronavirus diversity. Virus evolution, 3(1), vex012.
[5]. Grifoni, A., Sidney, J., Zhang, Y., Scheuermann, R. H., Peters, B., & Sette, A. (2020). A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2. Cell host & microbe, 27(4), 671-680.
[6]. Culliton, B. J. (1990). Emerging viruses, emerging threat. Science, 247(4940), 279-281.
[7]. Kim, J. A., Seong, R. K., & Shin, O. S. (2016). Enhanced viral replication by cellular replicative senescence. Immune network, 16(5), 286-295.
[8]. Latinne, A., Hu, B., Olival, K. J., Zhu, G., Zhang, L., Li, H., ... & Daszak, P. (2020). Origin and cross-species transmission of bat coronaviruses in China. Nature Communications, 11(1), 1-15.
[9]. Yuen, K. (2020). S, Ye Z-W, Fung S-Y, Chan C-P, Jin D-Y. SARS-CoV-2 and COVID-19: The most important research questions. Cell Biosci, 10(1), 40.
[10]. Koyama, T., Platt, D., & Parida, L. (2020). Variant analysis of SARS-CoV-2 genomes. Bulletin of the World Health Organization, 98(7), 495.
[11]. Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., ... & Qi, J. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell, 181(4), 894-904.
[12]. Padhi, A. K., & Tripathi, T. (2020). Can SARS-CoV-2 accumulate mutations in the S-protein to increase pathogenicity?. ACS Pharmacology & Translational Science, 3(5), 1023-1026.
[13]. Starr, T. N., et al. (2020). "Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding." Cell 182(5): 1295-1310. e1220.
[14]. To, K. K.-W., et al. (2020). "Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study." The Lancet Infectious Diseases 20(5): 565-574.
[15]. Padhi, A. K., et al. (2020). "High throughput designing and mutational mapping of RBD-ACE2 interface guide non-conventional therapeutic strategies for COVID-19." BioRxiv.
[16]. Tian, F., Tong, B., Sun, L., Shi, S., Zheng, B., Wang, Z., ... & Zheng, P. (2021). Mutation N501Y in RBD of Spike Protein Strengthens the Interaction between COVID-19 and its Receptor ACE2. BioRxiv.
[17]. Iwasaki, A., & Omer, S. B. (2020). Why and how vaccines work. Cell, 183(2), 290-295.
[18]. Mahase, E. (2020). Covid-19: Moderna vaccine is nearly 95% effective, trial involving high risk and elderly people shows. BMJ: British Medical Journal (Online), 371.
[19]. Callaway, E. (2020). COVID vaccine excitement builds as Moderna reports third positive result. Nature, 337-338.
[20]. Sharma, O., Sultan, A. A., Ding, H., & Triggle, C. R. (2020). A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Frontiers in immunology, 11, 2413.
[21]. Baraniuk, C. (2021). What do we know about China's covid-19 vaccines?. bmj, 373.
[22]. Jahromi, M. and M. H. Al Sheikh (2021). "Partial protection of Sinopharm vaccine against SARS COV2 during recent outbreak in Bahrain." Microbial Pathogenesis 158: 105086.
[23]. Knoll, M. D. and C. Wonodi (2021). "Oxford–AstraZeneca COVID-19 vaccine efficacy." The Lancet 397(10269): 72-74.
[24]. Mahase, E. (2021). Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant, British Medical Journal Publishing Group.
[25]. Badiani, A. A., Patel, J. A., Ziolkowski, K., & Nielsen, F. B. H. (2020). Pfizer: The miracle vaccine for COVID-19?. Public Health in Practice, 1, 100061.
[26]. Mahase, E. (2020). Covid-19: Pfizer vaccine efficacy was 52% after first dose and 95% after second dose, paper shows, British Medical Journal Publishing Group.
[27]. Thomas, K. (2020). "New Pfizer results: Coronavirus vaccine is safe and 95% effective." The New York Times 18.
[28]. Meo, S., et al. (2021). "COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines." Eur. Rev. Med. Pharmacol. Sci 25(3): 1663-1669.
[29]. 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.
[30]. Wang, Z., Schmidt, F., Weisblum, Y., Muecksch, F., Barnes, C. O., Finkin, S., ... & Nussenzweig, M. C. (2021). mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature, 592(7855), 616-622.
[31]. Adedokun, K. A., Kamorudeen, R. T., & Bello, I. O. (2021). Authorization of the first COVID-19 emergency vaccines: The matters arising. EXCLI journal, 20, 655.
[32]. Organization, W. H. (2020). "WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access." WHO: Geneva, Switzerland.

[33]. Perera, P. Y., & Perera, L. P. (2021). Development of leading first-generation vaccines against SARS-CoV-2. Microbes and infection, 104841.
[34]. Walsh, E. E., Frenck Jr, R. W., Falsey, A. R., Kitchin, N., Absalon, J., Gurtman, A., ... & Gruber, W. C. (2020). Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. New England Journal of Medicine, 383(25), 2439-2450.
[35]. Tenchov, R., Bird, R., Curtze, A. E., & Zhou, Q. (2021). Lipid Nanoparticles—From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS nano.
[36]. Sadarangani, M., Marchant, A., & Kollmann, T. R. (2021). Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nature Reviews Immunology, 1-10.
[37]. Bettini, E. and M. Locci (2021). "SARS-CoV-2 mRNA vaccines: immunological mechanism and beyond." Vaccines 9(2): 147.
[38]. De Soto, J. A. and F. DSSc (2020). "Evaluation of the Moderna, Pfizer/biontech, Astrazeneca/oxford and Sputnik V Vaccines for COVID-19."
[39]. Caga-anan, R. L., Raza, M. N., Labrador, G. S. G., & Metillo, E. B. (2021). Effect of Vaccination to COVID-19 Disease Progression. arXiv preprint arXiv:2103.02787.
[40]. Dai, L., & Gao, G. F. (2021). Viral targets for vaccines against COVID-19. Nature Reviews Immunology, 21(2), 73-82.
[41]. https://www.nytimes.com/interactive/2021/health/pfizer-coronavirus-vaccine.html
[42]. Koirala, A., Joo, Y. J., Khatami, A., Chiu, C., & Britton, P. N. (2020). Vaccines for COVID-19: The current state of play. Paediatric respiratory reviews, 35, 43-49.
[43]. Liu, C., Zhou, Q., Li, Y., Garner, L. V., Watkins, S. P., Carter, L. J., ... & Albaiu, D. (2020). Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases.
[44]. Locht, C. (2020). "Vaccines against COVID-19." Anaesthesia, critical care & pain medicine 39(6): 703.
[45]. Gerdil, C. (2003). "The annual production cycle for influenza vaccine." Vaccine 21(16): 1776-1779.
[46]. 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.
[47]. COVID, C., Team, V. B. C. I., COVID, C., Team, V. B. C. I., COVID, C., Team, V. B. C. I., ... & Trujillo, A. (2021). COVID-19 Vaccine Breakthrough Infections Reported to CDC—United States, January 1–April 30, 2021. Morbidity and Mortality Weekly Report, 70(21), 792.
[48]. Brown, T. "Pfizer's Major Setback in the COVID-19 Vaccine Race."
[49]. Madkaikar, M., et al. (2021). "India's crusade against COVID-19." Nature Immunology 22(3): 258-259.
[50]. Organization, W. H. (2021). Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing: interim guidance, first issued 8 January 2021, updated 15 June 2021, World Health Organization.