A Short History of Vaccines and the Rapid Development, Mechanism and Efficacy of the COVID-19 Vaccine

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Abstract

The first significant breakthrough in the use of vaccines to protect against infection was the development of the smallpox vaccine in 1796. Since then, there has been tremendous progress in scientific research and discovery that has led to the current arsenal of highly-effective vaccines that exist today. A vaccine is meant to train the body's immune system into remembering a specific bacteria or virus so as to be able to robustly battle against it. The immune system develops an immune memory, which is then used to rapidly respond to the pathogen and prevent it from causing disease.[1] Most traditional vaccines were originally based on a weakened or inactive form of a virus. The rise of the COVID-19 vaccine occurred in record time, gaining emergency use authorization (EUA) in just under a year. The power of mRNA-based vaccines was highlighted particularly through the widespread use of the Pfizer and Moderna COVID vaccines. While the mRNA-based vaccines are preferred, several other vaccines were developed through classical methods to protect against COVID. The variety of vaccines, while all effective, vary in their efficacy rates and protocols. There are specific side effects and risks that pertain to each vaccine. Even with multiple successful rounds of clinical trials and testing of the COVID vaccine, there is still a significant subset of the population who is against vaccination for personal, political or religious reasons. The rise of new variants of the virus and breakthrough cases among the already vaccinated present additional challenges that will drive future research in the field and fuel the race to come up with a pan-coronavirus vaccine.

I. History of vaccines

While COVID-19 is the current pandemic foremost in people's minds, there have been many previous disease outbreaks that the world has been faced with in the past. Smallpox, rabies, influenza, polio, measles, and the mumps are some pandemics that have emerged over previous centuries[2]. A need for a new vaccine arose with each successive outbreak.

A. Smallpox

Smallpox, caused by the variola virus, first appeared in China in the 4th century and spread quickly thereafter. The initial symptoms of smallpox are a high fever, head and body aches, and occasional vomiting. Rashes and sores are the most characteristic of smallpox and it spreads and evolves into pustules all over the body. The majority of those infected with smallpox are able to recover, however, 3 out of every 10 people who contract the disease die. [3] There were about 300 million deaths as a result of smallpox in the 20th century.[2] In the 16th century, the first attempted method for treating the disease was introduced. Variolation is the process of exposing uninfected people to smallpox sores through their arm or nose. This would cause the symptoms of smallpox but would not result in death as often. However, in 1796, there was progression in the treatment of smallpox and vaccination efforts began. Dr. Edward Jenner observed milkmaids who were infected with cowpox and found that they were also protected from smallpox. After seeing the effects of variolation, Dr. Jenner believed that exposure to cowpox could be an effective way of preventing smallpox infection. His theory proved successful in trials and vaccination was widely accepted[3]. The word vaccine, or vaccination, stems from Dr. Jenner's cowpox discovery. In

Latin, the word ‘cow’ translates to ‘vacca.’ *Vaccinus* is the Latin word for ‘from cows.’ Cowpox was a large contributor to the beginning of using weakened forms of a virus as a form of vaccination. Consequently, it is fitting that the word vaccine originates from the word cow.[4]

The smallpox vaccine is composed of a live form of the virus vaccinia. This virus is a poxvirus that resembles smallpox, yet is less harmful. The vaccine displayed a 95% efficacy rate amongst all those who were vaccinated. Moreover, when the vaccine was administered after exposure to the variola virus, a prevention or reduction of infection was observed. The vaccine can remain effective for three to five years until its efficacy noticeably decreases. A booster vaccine is necessary in order to maintain long-term immunity.[3]

B. Rabies

Rabies is a virus that is transmitted through the bite from a rabid animal. [5] The early symptoms of rabies include weakness, discomfort, fever, or headaches. These symptoms can evolve into cerebral dysfunction, anxiety, confusion and agitation. [6] In 1885, Louis Pasteur made a significant discovery in vaccines through his study of the rabies virus. Pasteur observed rabbits’ spinal cords that had been inoculated with the rabies virus and desiccated for 15 days. He found that the rabbits were no longer infectious after the 15-day period. Pasteur then tested his discovery by inoculating desiccated spinal cords into nine-year-old Joseph Meister who had been attacked by a rabid dog. This decision saved Meister’s life and demonstrated the benefits of creating vaccines from inactivated forms of the virus, which influenced the development of many future viruses. [7]

The rabies vaccine can be administered both before and after exposure. On the day of one's exposure to rabies, doses of human rabies immunoglobulin and a vaccine are administered. On Days 3, 7, and 14 following the exposure an additional dose of the vaccine is given. However, for those who work in an environment where rabies is prevalent, the vaccine administration process is slightly different. They should obtain the vaccine before having a direct exposure to rabies. Three vaccine injections should be given on Days 0, 7, and 21 or 28. Moreover, someone with constant exposure to rabies must have their antibodies tested every six months in order to determine the need for a booster dose. [5]

C. Influenza

Influenza, otherwise known as the flu, was first documented in 1580. However, there have been many significant outbreaks of the flu since its initial appearance on the scene. In 1918, the Spanish flu pandemic erupted. [8] The H1N1 flu strain was responsible for this virus. Without a proper treatment for the flu, isolation was required and masks were encouraged. This pandemic was responsible for over 20 million deaths worldwide. In search of a solution, Dr. Edward C. Rosenow of Mayo Clinic created a flu serum. The serum consisted of a mixed vaccine, which included bacteria that cause pneumonia. After administering the serum, Dr. Rosenow observed that no harm was done to the patients and he claimed that the serum could be a source of protection. It was later found that the serum did not function entirely as a flu vaccine, but rather protected people from pneumonia following their flu infection.[3]

English scientists successfully isolated the influenza A virus in 1932 -1933 by using patients' nasal secretions. This isolation was the spark for many subsequent discoveries that helped develop the vaccine. The first flu vaccine was composed of inactivated influenza A virus. Following studies done in 1942, it was proven that a vaccine made of an inactivated form of the virus could successfully protect against the flu. [9] Although there are many variations and strains of the flu virus, each vaccine attempts to protect against as many strains as possible. According to Dr. Rachael Lee of UAB Medicine, the flu vaccine of 2020-21 included four strains of the virus that were flagged by the World Health Organization for special attention.[10] However, one vaccine cannot protect against all possible strains of the virus and therefore it is crucial to receive a flu shot annually. Although the vaccine triggers the production of antibodies against the virus, these levels may decline over time. An annual flu shot will boost antibody titers and help protect against new strains. [11]

D. Polio

Polio, caused by the poliovirus, is a disease that results from viral invasion of the brain and spinal cord, ultimately leading to paralysis.[12] Although polio has since been largely eliminated, there were many epidemics that occurred in the period from 1948-1955. Similar to the precautions against influenza, public gatherings were avoided and those who were infected had to be isolated. The first polio vaccine became available in 1955, after years of dedicated research led by Dr. Jonas E. Salk and colleagues. [2] Since the year 2000, inactivated polio vaccine was the only type being administered. The CDC recommends that one obtain four doses of the vaccine at the ages of 2 months, 4 months and then between 6 to 18 months and 4 to 6 years of age.

Vaccination as a child has a very high efficacy and will not need to be renewed or boosted as one ages.[12]

E. Mumps

The mumps peaked nationally in the United States in 1968 with 152,000 reported cases. [13] The disease is primarily marked by swelling of the salivary glands just below the ear, but also produces a low-grade fever and respiratory problems. Mumps is transmitted through respiratory droplets or via contaminated surfaces.[14] With new disease outbreaks in the late 1960's came a pressing need for a vaccine. However, unlike previous vaccines, the developmental process took a very quick four years.[15] Dr. Maurice Hilleman was approached by his daughter with a sore throat which he subsequently diagnosed as the mumps. Hilleman knew of a research lab that had just recently licensed a measles vaccine after growing a weakened form of a live virus in chicken embryos. He thought that this technique could also be used for the mumps. Dr. Hilleman swabbed his daughter's throat and used the resulting sample to develop a vaccine in 1967. [16]

Hilleman's vaccine, known as the MMR vaccine, also serves as protection against the measles and rubella. According to the CDC, two doses should be administered to patients. The first dose should be administered at around 12 to 15 months and the second dose should be given once the patient is between the ages of 4 and 6. With two doses, the mumps vaccine displays an 88% efficacy rate in preventing the disease. When only one dose is obtained there is a 78% efficacy rate. In the case of a mumps outbreak, a third dose could be recommended.[12]

II. Process for Vaccine Development

Developing a vaccine is a very thorough process that traditionally takes between 10 to15 years.[17] Research on the pathogen structure, disease epidemiology, and clinical features is crucial in identifying an antigen that can produce the immunological response necessary to protect against the disease. When developing a new vaccine, the effectiveness in target populations must be determined. This can usually be measured using animal models which can closely resemble disease in humans. Before entering into clinical trials, a vaccine is evaluated on the basis of its host-pathogen interaction, protective immune mechanisms, and antibody response. Additionally, in order for the vaccine to be finalized, it needs to be tested for dose toxicity, immunogenicity, pharmacodynamics, pharmacokinetics, and local tolerance. [1]

Following finalization of the preclinical vaccine, the three stages of clinical trials are performed. The first stage focuses on the safety of the vaccine. [1] In this stage, the vaccine is administered to a small group of healthy individuals so as to evaluate safety, the proper dosage, and the immune response. The second stage is a more expanded trial, which focuses on a larger sample population. Hundreds of people receive the vaccine and safety, appropriate dosage, and immune response are again evaluated. During this phase, it is officially confirmed that the vaccine is safe and immunogenic. The third trial evaluates clinical efficacy. This trial is performed on the largest scale as the vaccine is administered to thousands of people. Efficacy is determined by the percent decrease of disease incidence in vaccinated people. [18]

These trials are typically conducted on healthy human volunteers by exposing them to the pathogen after being vaccinated for the disease. Throughout the clinical trials, safety is of the utmost importance and is continuously monitored. Any pain, redness, swelling, or fever that arises after being vaccinated is recorded. The vaccine might need to be limited to certain populations based on the side effects that are present during trials. When administered a new vaccine, the individual might experience a variety of different reactions. Each patient's response to the vaccine must be studied in order to confirm whether it is coincidental or directly correlated with the vaccine given. [1]

The preclinical and clinical trial results, as well as information regarding the physical and chemical properties of the vaccine, are all compiled into a report that will be used to apply for registration of the vaccine. After officially licensing a vaccine, public health authorities can recommend it to the public. However, it is still crucial that the safety and effectiveness of the vaccine is carefully monitored.[1]

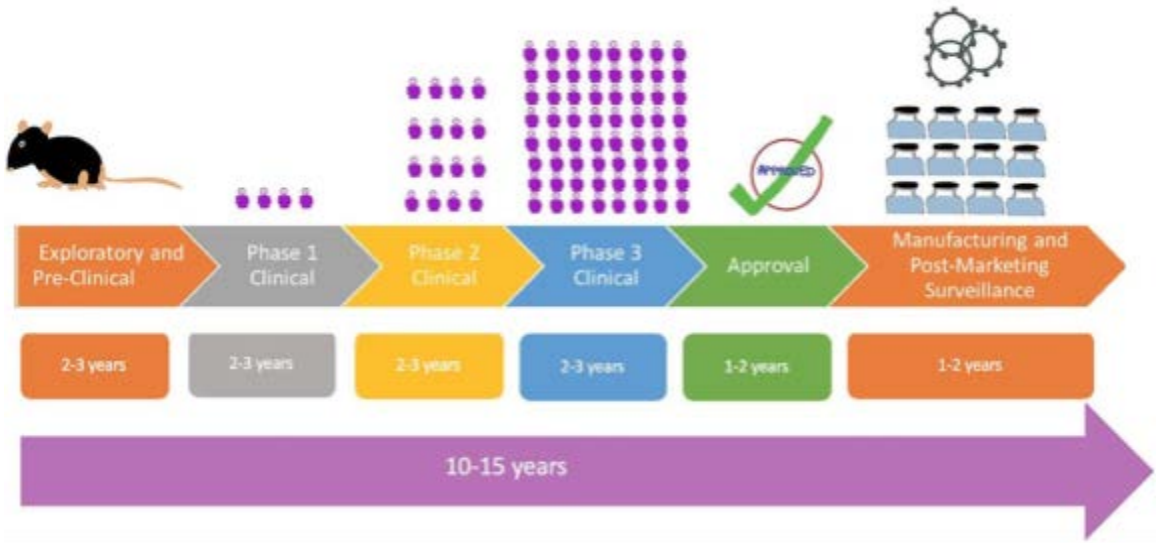

Figure 1
Normal Process of Vaccine Development

III. Rise of COVID-19 and the Need for Rapid Vaccine Development

While the COVID-19 pandemic was officially declared by the World Health Organization on March 11, 2020, the rise of the virus started a few months prior. At the tail end of 2019, several viral pneumonia cases were discovered in the Hubei province of China. By January 10th of 2020, the genome of the new coronavirus was fully sequenced. This novel virus was later renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was found that the virus could be transmitted from person-to-person and that those who were asymptomatic could still infect others. On January 30, 2020, SARS-CoV-2 was declared by the WHO as a Public Health Emergency of International Concern. At the end of February 2020, there were already 83,652 cases of COVID-19 registered globally. [19]

The quick rise of COVID-19 necessitated the design of a vaccine that could be tested and administered as soon as possible. The SARS-CoV-2 virus structure and behavior was the primary focus in early vaccine development. On March 16 2020, the first clinical study of the COVID vaccine was performed, just under two months after genomic sequencing of SARS-CoV-2. [19]

IV. Fast Vaccine Development

Prior to COVID, the fastest vaccine to ever be developed was that for mumps, a process which took four years.[15] The development of the COVID vaccine stands in stark contrast to previous vaccinations. SARS-CoV-2 was first discovered in December of 2019 and was soon after identified as the virus that causes COVID.[20] Less than a year passed before the Moderna and

Pfizer vaccines were approved for emergency use by the CDC and the first shots were given in December 2020. [21]

This fast-paced development of the vaccine can be attributed to several factors. The primary reason is because prior research already existed on the SARS-CoV-2 virus. This is due to the fact that this category of coronavirus is responsible for more than the COVID-19 pandemic being the cause of common colds, the Severe Acute Respiratory Syndrome (SARS) epidemic and the outbreak of Middle East Respiratory Syndrome (MERS). Evidently, SARS-CoV-2 has been around for a long time and exists in a variety of forms. According to Dr. Eric J. Yager, coronaviruses have been studied for over 50 years. Consequently, there was considerable data on their structure, genome and life cycle already available at the start of the COVID crisis. The severity of the pandemic also encouraged worldwide collaboration, which is not always a given in the field of science. Researchers around the world largely shared their data on the rapidly spreading coronavirus with other scientists. This collaboration allowed for the necessary research and clinical trials to be put into action much faster. [20]

While the development of a vaccine usually follows a series of strictly-regulated steps, the urgent COVID-19 situation required that the process be greatly accelerated. In normal vaccine development, Phases 1 and 2 are performed separately, with the population size increasing in subsequent phases. However, the dire need for a COVID vaccine caused phases 1 and 2 to be combined and the experimental group was larger than usual. Moreover, the approval process was quickened in order to allow for emergency usage. [18]

Figure 2.
Accelerated Vaccine Development

V. Vaccine Hesitancy

According to the World Health Organization, vaccine hesitancy is a threat to global health and reduces the possibility of reaching herd immunity. [22] In a survey conducted amongst U.S. adults who are 18 years and older, 17.7% of the 1219 respondents claimed that they would not receive a vaccine and 24.2% were still unsure. There is even hesitancy amongst health care workers, which in turn negatively influences the many people who turn to them for advice and direction.[23] All of these factors will cause people to refrain from becoming vaccinated. [22]

Another study evaluated 991 responses to an online survey and found that 10.8% would not receive the vaccine and 31.6% were still undecided. The highest rates of vaccine hesitancy were discovered among women, blacks and Latinos and those below the age of 60. Vaccine hesitancy also correlated with lower levels of education and household income. Such surveys are important in deciding where vaccine promotion campaigns should be focused in the future. The study found differences in the reasoning behind those who were hesitant and those who were adamant as to not being vaccinated. The unsure group's reasoning pertained to safety and efficacy concerns,as well as desire for more information and knowledge. Within the group that felt strongly about not obtaining the vaccine, their reasoning stemmed from anti-vaccine beliefs, attitudes, and emotions. The participants in the survey had numerous specific reasons for their hesitancy. People had concerns regarding unsafe side effects, the rapid development and short trial period of the vaccine and its relative newness. They also expressed a lack of trust in the government and agencies like the CDC. Religious beliefs were another leading cause of hesitancy. As one participant responded, "God protects his children from viruses." Due to the large and diverse sample size of the survey, the results are able to be generalized to see distinct trends on a national level. [24]

Personal interviews that I conducted with two home health aides (HHA) illustrate some of the concerns of those with vaccine hesitancy. S.D, a 36-year-old female who was born in Jamaica, is currently living in the Bronx. She has not taken any of the COVID vaccines, despite being vaccinated for many other diseases. Because she has not been vaccinated, S.D. is unable to continue her work as a HHA. Consequently, she has thought about becoming vaccinated despite

her continuing hesitancy. She feels that the vaccine was developed extremely fast and that there was a big rush to become vaccinated once it became available to the public. This speed and pressure was seen not only in the development of the vaccine, but also in the requirement for a second dose and even booster shots and S.D is bothered by all these factors.

D.D, a 68 year old female who was also born in Jamaica, currently resides in Brooklyn. She has been in the United States for 30 years and she has only taken the flu vaccine once. D.D. states, "It made me sick. I could not walk and I never took it again." She is not comfortable taking the COVID vaccine and her preferred choice of treatment is natural remedies. D.D.s had further concerns regarding the short development time of the vaccine and the reported side effects of the shot. She feels very strongly about refraining from vaccination and has been granted a religious exemption in order to continue working as a home health aide.

VI. Makeup of the Covid Vaccine

A critical factor in the design of the COVID vaccine was the determination of the coronavirus ribonucleic acid (RNA) sequence in early January 2020. Scientists had been studying vaccines based on viral genomes and proteins and immediately utilized that knowledge in the battle against COVID-19. Messenger RNA is typically used by living cells as a template to synthesize proteins. DNA is transcribed into mRNA, which then dictates protein production. [21] A mRNA vaccine functions by introducing a segment of mRNA that corresponds to the viral protein. In the case of the COVID-19 vaccine, the mRNA codes for the spike protein (S protein) and will trigger its production. [25]

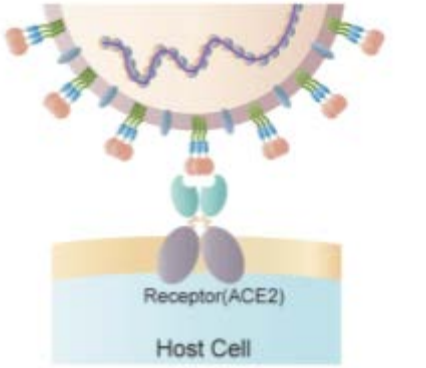

Figure 3.
Binding of the Spike Protein to the Cell Surface Receptor.

The S protein is pivotal to the virus' ability to infect a host cell. [21] S proteins coat the surface of the SARS-CoV-2 virus and will bind to the angiotensin-converting enzyme 2 receptor on the target cell.[26] Because of the S proteins' crucial role in entering the host, it is a perfect focal point for designing a vaccine to prevent infection.

Upon production of the S protein by the mRNA segment, it is then displayed on the cell surface and then recognized by the immune system. Consequently, the immune system will produce antibodies in order to fight off an infection. While the S protein produced through the vaccine is not harmful, the production of antibodies serves to train the immune system.[27] The body will retain immune memory against possible future viral infection.[25]

The mRNA vaccine is surrounded by a liposome and a complexing agent. This aids in the transport of the vaccine to the cytoplasm of the cells and the lipid coating allows the vaccine to cross the lipid bilayer of the plasma membranes more efficiently. Moreover, the liposome will

help protect the mRNA from degradation prior to reaching the target cells. [21] The mRNA is degraded once it enters the cytoplasm and is translated into the proper proteins to generate an immunological response. [28]

VII. Vaccines in the United States

A. Pfizer- BioNTech (BNT162b2)

The FDA fully approved the Pfizer vaccine in August 2021 for those who are 16 years of age and older. [29] Prior to that, the FDA had conferred Emergency Use Authorization (EUA) status on the Pfizer vaccine in December 2020 and thus made it widely available to the general population. Pfizer's vaccine is composed primarily of mRNA, which is the active ingredient. However, the vaccine also includes lipids, salts, and sugars. The lipids serve as a protective barrier for the mRNA and contribute to easier passage through the cell membranes. Salts such as potassium chloride and dibasic sodium phosphate dihydrate are critical in balancing acidity within the body. The sugar component aids in maintaining the shape of the molecules during the freezing of the vaccine for transport and storage. [30]

Pfizer's protocol stated that one should obtain two shots, spaced 21 days apart. The vaccine was determined to reach maximal efficacy two weeks after the second shot. Typical side effects observed upon vaccination included pain, redness, and swelling at the injection site. Other possible side effects are fatigue, headaches, muscle aches, chills, fever and nausea. Serious side effects, such as anaphylaxis, can also occur on rare occasions. According to the FDA, there is a

remote possibility of developing myocarditis and pericarditis in adolescents and young adults. The CDC recommends that waiting eight weeks between the two doses might reduce this risk. [29]

B. Moderna (mRNA-1273)

The Moderna vaccine received full FDA approval for those who are 18 years and older in January 2022.[29] This was an upgrade from its initial EUA, which was enacted a week after Pfizer's in December 2020. Moderna's vaccine is very similar to the Pfizer vaccine in many respects, primarily that the predominant component of the vaccine is the mRNA. Additionally, there are lipids that assist in delivering the mRNA to the cells. The remaining components of the vaccine are acids, acid stabilizers, salts, and sugars, all of which serve to maintain the vaccine's stability. [30]

Moderna requires two shots, administered 28 days apart. This is a week longer than Pfizer's wait time. [29] The difference in spacing between doses is not particularly significant, as this is simply how the vaccines were originally given during the clinical trials.[31] The side effects of this vaccine are relatively identical to those that arise after obtaining the Pfizer version. Moreover, the FDA also warned of the small risk of developing myocarditis and pericarditis from Moderna.[29]

The period in between doses for both the Pfizer and Moderna vaccines is significant in stimulating the immune system to produce the most effective response. A small immune reaction is initiated following the first dose. The time in between the two doses allows the immune

system to develop its response properly. According to the CDC, one can receive their second dose no more than four days before the recommended time. [32]

C. Johnson and Johnson (Ad26.COV2.S)

The Johnson & Johnson vaccine diverged from the Pfizer and Moderna model and was FDA approved in February 2021. This variation is a viral vector vaccine.[29] In a viral vector vaccine, a modified virus is used as a means of delivering instructions to the host cell.[33] For the COVID vaccine, an adenovirus is used as the vector. The adenovirus is modified so that it cannot perform normal viral functions such as causing sickness, replicating and/or becoming integrated into the host DNA. In place of the original adenovirus sequence, a genetic segment of the COVID virus is inserted into the adenovirus DNA. This segment specifically codes for the COVID spike protein. [34] Once the adenovirus vector enters the cell, the viral capsid disintegrates and the DNA segment proceeds to the nucleus. The DNA is transcribed into mRNA and then translated into the spike protein. The spike protein will then emerge on the surface of the cell in order to initiate an immune response and trigger antibody production. The goal of the Johnson & Johnson vaccine is the same as its counterparts from Pfizer and Moderna, but the mechanism for achieving that goal is different. [30]

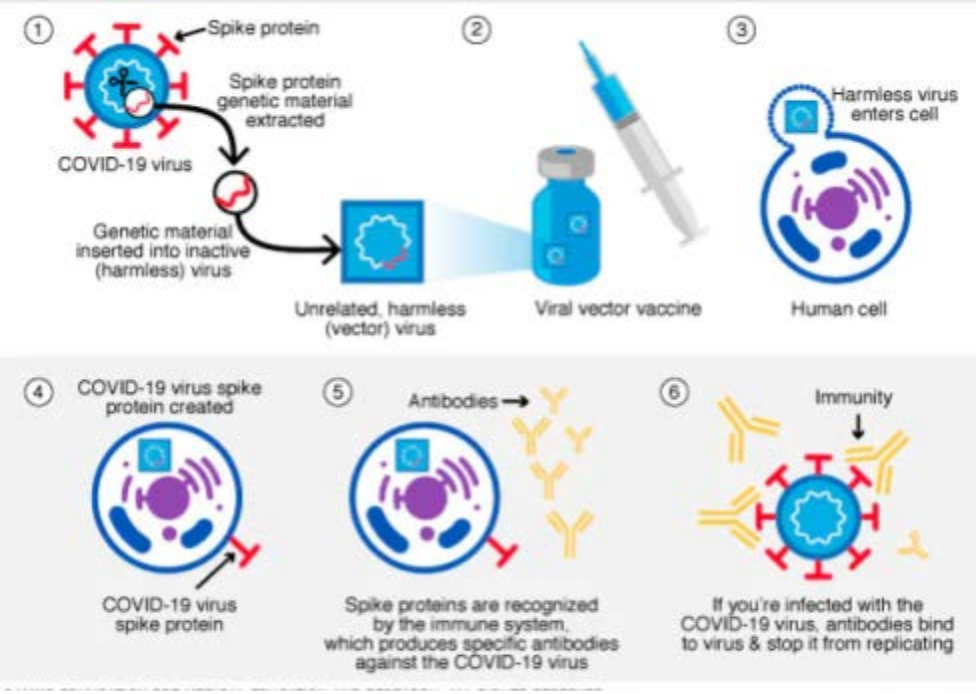

Figure 4. Mechanism of Viral Vector Vaccines.

The most significant difference in the makeup of the J&J vaccine is the presence of the adenovirus in place of a strand of mRNA. Adenovirus type 26 (Ad26) is the primary component of the vaccine. The remaining "packaging" ingredients are acids, salts and sugars, which have the same function as in the Pfizer and Moderna vaccines. [30]

Only one shot is required according to Johnson & Johnson's protocol. This makes the vaccine both easier to administer, as well as more convenient for the general population. [29] According to Dr. Monica Gandhi, an infectious disease specialist at UC San Francisco, the vaccine progressed through trials showing that only one dose produced a very strong immune response. The antibody levels were high even after only a single dose and therefore a second dose was not

needed. [35] Furthermore, the J&J vaccine does not require special equipment to store and can be kept in a regular refrigerator, remaining stable for a significant period of time. [34]

There are dangerous, yet rare, side effects that have been associated with the Johnson and Johnson vaccine. A new health condition called Thrombosis with Thrombocytopenia Syndrome (TTS) has been seen in four out of one million people who have received this version of the vaccine. Thrombosis is the formation of blood clots. [37] Thrombocytopenia occurs when one has a low platelet count. These platelets aid in the formation of clots.[38] This rare side effect of the vaccine can be recognized by symptoms such as severe headaches and blurred vision, shortness of breath, chest pain, leg swelling, abdominal pain and easy bruising. [39] After the discovery of six cases of TTS, a pause in the J&J vaccine administration was recommended by the FDA and CDC. These agencies greenlighted the resumption of Johnson and Johnson vaccinations based upon reevaluation of the available data in light of the very miniscule number of TTS cases. [40]

VIII. Vaccines Globally

A. Oxford-AstraZeneca (AZD1222)

The Oxford-AstraZeneca vaccine, while not available in the U.S, has been granted emergency use authorization for countries in the European Union and the United Kingdom. Some of the major distinguishing factors of this vaccine are its significantly reduced cost and the fact that it can be stored in a regular refrigerator. Two doses of the vaccine are required within 4 to12 weeks of each other. [29]

Although not approved in the U.S, AstraZeneca utilizes the same mechanism of action as the Johnson and Johnson vaccine. It is a viral vector vaccine that uses a harmless adenovirus to deliver the genetic code for the spike proteins into the cells. Once the spike proteins are manufactured and presented on the surface of the cell, an immune response is triggered. [29]

The side effects of AstraZeneca are usually not too severe. In rare cases, the vaccinated individual might develop blood clots as well as low blood platelets or TTS. The vaccine prevented hospitalizations, ICU patients, and death and these significant advantages greatly outweighed the relatively small risk of blood clots. [41]

B. Novavax (NVX-CoV2373)

The Novavax vaccine is a protein-based vaccine that is combined with an adjuvant. [42] An adjuvant is a component in certain vaccines which assists in the immune response of those receiving the vaccine. [43] On February 3 of 2022, the Novavax vaccine was conditionally approved in Great Britain for those 18 years of age or older.

NVX-CoV2373 serves as the spike protein which combines with the Matrix-M adjuvant. This vaccine produces a very strong immune response from both B-lymphocytes and T-lymphocytes.[42] Two doses of the Novavax vaccine are needed, with a three-week wait period in between shots. [29]

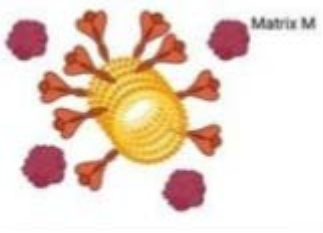

Figure 5. Structure of the Novavax Vaccine

An advantage of the Novavax vaccine is its stability and ability to be stored at refrigerated temperatures for long periods of time. This vaccine is more traditional in design than the newer mRNA vaccines and might appeal to those who are hesitant about the Pfizer and Moderna versions. Novavax also has the added benefit of being safer for pregnant women. [42]

IX. Efficacies of the Vaccine

A. Pfizer- BioNTech

When the Pfizer vaccine was proceeding through clinical trials, it exceeded all expectations for its success and displayed a 95% efficacy by the 3rd phase. Despite these strong levels of efficacy, it was also discovered that the effectiveness will decrease over time.[29]

The 95% efficacy rate is representative of both participants who have not contracted SARS-CoV-2 and participants who have previously had the COVID virus. In one specific trial, Pfizer observed 170 cases of COVID-19. 162 of these cases were seen in the placebo group that had not been given the vaccine. The eight remaining cases of COVID came from the BNT162b2 group that had been vaccinated. Out of the 10 severe cases of COVID, only one case was observed in the vaccinated group and the remaining nine cases were from the control group. [44]

Pfizer's Data Monitoring Committee analyzed data on at least 8,000 participant's reactions to the vaccine in the final phases of clinical trials. The committee observed that most patients tolerated the vaccine very well. The unfavorable effects of the vaccine were usually resolved a few days

after the shot was administered. They did find that fatigue appeared with 3.8% frequency and headaches presented with 2% frequency. [44]

B. Moderna

Similar to the Pfizer vaccine, the Moderna vaccine displayed a 95% efficacy in phase 3 of clinical trials.[29] While the efficacy rates for Moderna and Pfizer are essentially the same, research has found that there is a slightly lower risk of contracting COVID-19 when vaccinated with Moderna. Two groups of 219,842 U.S. veterans were analyzed after receiving either the Pfizer or Moderna vaccine. The results displayed that there was a 5.75 per 1,000 person risk of infection for the group vaccinated with Pfizer. There was a 4.52 per 1,000 person risk of infection for the group vaccinated with Moderna. Those who were vaccinated with Pfizer had a 27% greater risk of becoming infected. Dr. J.P. Casas, an epidemiologist and professor at Harvard Medical School, states, "regardless of the predominant strain of COVID– Alpha earlier and then Delta later – Moderna was shown to be slightly more effective." [45]

C. Johnson & Johnson

The efficacy of the Johnson and Johnson vaccine showed around a 30% decrease both two weeks and four weeks post vaccination. A 67% efficacy rate against infection was measured 14 days after vaccination, whereas a 66% efficacy rate was seen 28 days after vaccination. [29] Despite this 30% decrease, the J&J vaccine was still extremely effective in preventing serious illness and death In the clinical trials for Johnson and Johnson, there were 16 hospitalizations and seven

fatalities within the placebo group. The vaccinated group recorded zero hospitalizations and deaths, displaying a 100% efficacy rate in these categories. While the J&J vaccine was not as effective for mild and moderate cases of COVID, none of these test subjects required medical assistance. [35]

D. Oxford-AstraZeneca

During the 3rd phase of clinical trials in March of 2021, efficacy of the vaccine was measured. 15 days after being administered a dose of the Oxford-AstraZeneca vaccine, a 76% efficacy rate was observed in its ability to prevent symptomatic disease. More importantly, the vaccine displayed 100% efficacy in preventing serious illness. Even in patients over the age of 65, an efficacy of 85% was noted. [29] The vaccine was just as effective in preventing hospitalization due to COVID. [46]

E. Novavax

The Novavax vaccine proved to be 90% effective in preventing symptomatic infection and displayed 100% efficacy in preventing moderate and severe disease. [29]

X. Breakthrough Infections

While COVID-19 vaccines have a high efficacy rate, they are not 100% effective and will not prevent all infection. The purpose of the vaccine in these situations is to prevent one from

developing serious illness. Those who are vaccinated and contract the virus can still develop symptoms, however, the symptoms will likely be less severe. Consequently, there will be less hospitalization and deaths. [47]

XI. Antiviral Medication

In the event that one does contract COVID, whether they are vaccinated or not, there are new treatment options that could prevent the virus from becoming severe. In December of 2021, Pfizer's oral pill, otherwise known as Paxlovid, was granted emergency use authorization (EUA) by the FDA. The medication is meant to protect against a progression of the virus into a severe infection. Its target population are adults and children at least 12 years of age and older who have contracted a mild-to-moderate form of COVID and are at high risk for becoming more seriously ill. Paxlovid is designed for use once an individual has already been infected, not for pre or post exposure. One should take three tablets twice a day for a period of five days. The pill is composed of two drugs, nirmatrelvir and ritonavir. Nirmatrelvir hinders the coronavirus' replication, while ritonavir slows the breakdown of nirmatrelvir in order to extend the period of time that it exists in the body. The trials found that the hospitalization and deaths that arose from COVID decreased by 88% when Paxlovid was given to patients. [48]

XII. The Rise of New Strains

During the spread of COVID-19, the world has been faced with many new strains and variations of the virus. New strains arise as a result of mutations to the viral genome. Some strains that have

developed over the past two years are the alpha, beta, gamma, delta and omicron variants. These strains all fall under the category of variants of concern, as they can be more infectious and less likely to be hindered by vaccines. When a new variant emerges, the immediate question on people's mind is whether the already existing vaccines will still have the same efficacy. [49]

While most variants are sources of concern and require investigation, the delta and omicron variants were particularly problematic in the U.S. [50] The delta variant was detected in the United States in March 2021 and was responsible for over 80% of new COVID cases, exhibiting a very high transmission rate. [51] In November 2021, the omicron variant materialized and began its rapid spread. This variant was responsible for the largest surge since 2019 and was extremely contagious. [49] These variants result from mutations to the spike protein, which is crucial to the proper functioning of the vaccine. Consequently, mutations to the spike protein raise the question of whether the vaccine can maintain its full efficacy. [52]

XIII. The Effect of New Variants on Vaccine Efficacy

The CDC states that the Pfizer, Moderna, and Johnson and Johnson, vaccines authorized for use in the United States all effectively protect against the delta variant.[51] According to one study, Pfizer's vaccine was found to be 88% effective against the delta variant. This is still very effective, but is a marked 6% decrease from its original efficacy. [53] The Moderna vaccine was found to be 86.7% effective in preventing infection and an even higher efficacy rate of 97.5% was seen in preventing hospitalization. [54] The J&J vaccine does not prevent infection by the delta variant, but it clearly reduces the severity of the disease. It was also 71% effective against

hospitalization and displayed a 95% efficacy rate against death. [55] When one is vaccinated with two doses of Astrazeneca, the efficacy against the delta variant is 60%. [53] In a study done on the efficacy of the Novavax vaccine while the delta variant was the prevalent strain of COVID, a 90% efficacy rate against mild, moderate, and severe disease was observed. [56] Although there were slight reductions in vaccine efficacy rates against the delta variant, they still provided significant protection.

According to the CDC, both the Pfizer and Moderna booster shots can protect against hospitalizations due to the omicron variant. [29] In a study done on Qatari residents, it was found that when vaccinated with two doses of either the Pfizer or Moderna vaccine, they were protected from symptomatic infection by the omicron strain of COVID-19. [57] The Johnson and Johnson booster shot notably displayed an 85% efficacy in reducing hospitalizations. According to Novavax, their vaccine is able to produce a strong immune response against the omicron strain. [29] Dr. Laith Abu-Raddad, an infectious disease and epidemiology expert at Weill Cornell Medicine-Qatar, suggests that these many variants require a concerted effort to develop universal pan-coronavirus vaccines. [57]

XIV. Need for a Booster

In September of 2021, the FDA expanded Pfizer's emergency use authorization of the vaccine to include a booster dose. In explaining the need for a booster, the FDA observed the rates of COVID-19 infection amongst different categories of people during the delta variant outbreak. The FDA compared those who had completed their dosage of the vaccine earlier and those who

completed their dosage later. It was noted that in July and August of 2021, COVID-19 was more prevalent in those who had been fully vaccinated earlier in the year. This evident breakthrough of COVID-19, despite being vaccinated, emphasized the fact that efficacy rates will decrease over time. [58] The purpose of a COVID booster is to maintain a high level of protection after the original dosage wears off. [59]

Each of the vaccines has its own protocol specifying which age groups are eligible and the time intervals that should be followed when obtaining the booster. According to Pfizer-BioNTech, after five months of being fully vaccinated, all those 12 years of age and older can receive the booster. Moderna states that anyone over 18 should receive the booster after a minimum of five months following the original two doses. Johnson & Johnson's instructions specify that anyone over 18 years of age can receive a booster shot two months after their initial vaccination. [60]

According to the CDC, one's booster dose does not need to be the same vaccine that the patient obtained originally. In fact, the CDC recommends that people should attempt to receive the mRNA boosters, either from Pfizer or Moderna. This is due to severe side effects that could result from the J&J vaccine. For those between the ages of 12 to 17, the Pfizer vaccine is the only booster approved and available to them. [60]

On March 29, 2022, the FDA gave official authorization for a second booster shot, obtained either from Pfizer or Moderna. This dose was intended for the older population, as well as those who are immunocompromised. Individuals 50 years of age and older are eligible to obtain the second booster shot within a minimum of four months after receiving their first booster. They

can receive either Pfizer or Moderna. Immunocompromised individuals over the age of 12 can also receive a second booster dose of the Pfizer vaccine at least four months subsequent to their initial booster shot. Lastly, the second booster dose of the Moderna vaccine is available to immunocompromised individuals who are at least 18 years old and are four months post their initial booster. [61]

XV. Halachic Considerations

Halachic considerations regarding the COVID vaccine were discussed in an interview I conducted with Rabbi Elliot Schrier, previously a rabbi at the Albert Einstein College of Medicine and currently the pulpit rabbi of Congregation Bnai Yeshurun in Teaneck, New Jersey. According to Rabbi Schrier, the primary halachic concern is taking proper measures to guard one's life. In Sefer Devarim it states, "ונשמרתם מאוד לנפשותיכם". This translates to "For your own sake, therefore, be most careful." This serves as a proof text in displaying that halacha values life. According to the Sefer Hachinuch, one is not only supposed to protect themselves from life ending situations but also from anything that will cause damage. This comes up in many instances in Judaism. If a person's life is in danger, it is permissible to call an ambulance or drive them to the hospital even on the Sabbath. Additionally, one can be exempt from fasting on designated days such as Yom Kippur if experiencing serious health issues. Evidently, in the case of obtaining the vaccine, one should value the strong significance halacha places on protecting a life. Major poskim (arbiters of Torah law) in the Modern Orthodox community, such as Rav Herschel Schachter and Rav Mordechai Willig, have recommended that people get vaccinated.

XVI. Future of the Vaccine

Since the COVID-19 first broke out, there have been many developments that have largely contributed to the fight against infection. As a result of extensive research, the information available on genetics, virology, and immunity has grown tremendously. While guidelines and protocols have evolved to become more lenient, the virus is still prevalent. It is crucial to evaluate the future of the vaccine and how effective it will continue to be. [62]

In an interview I conducted with Rabbi Dr. Aaron Glatt, Chief of Infectious Diseases at Mount Sinai South Nassau Hospital in Oceanside, Long Island, he discussed his view on the future of the vaccine and COVID-19 as a whole. When asked about whether he predicts more variants to develop and how efficacy rates could resultantly change, Rabbi Dr. Glatt explained that it is extremely difficult to predict the future of the vaccine. He continued by saying that it is almost a guarantee that there will be new strains in the future, however, its significance in terms of the efficacy of the vaccine is unknown. Rabbi Dr. Glatt gave strong praise to the vaccines, particularly the mRNA-based vaccines, and claimed that everyone should be vaccinated. If people want to be protected from the virus, vaccination is the way to obtain that. In the uncertain time of COVID-19, it is natural that everyone is looking for answers. However, as Rabbi Dr. Glatt stated, “We really can’t predict what the future will be and we’ll have to wait and see.”

XVII. Conclusion

Vaccines have significantly progressed since Dr. Edward Jenner's first contributions in 1796. A process that once took a minimum of 10 to15 years was successfully condensed into an incredible time span of just one year. Advances in genetic engineering allowed for the quick sequencing of the viral mRNA and the subsequent development of the vaccine. The novel COVID vaccine has saved many lives and reduced severe infection and hospitalizations. Despite these promising results, there are still populations who refuse to be vaccinated, hindering the possibility of reaching herd immunity. Although the COVID vaccine was significantly different in design and speed of development from previous vaccines, it will not have maximal efficacy until people learn to understand and accept these changes. The now revolutionary speed of vaccine development will play a vital role in managing any future pandemics.

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