Understanding COVID-19 Vaccine Development and Impact

By

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A project submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

Department of Pharmacy
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April 2024

Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Understanding COVID-19 Vaccine Development and Impact'' submitted by Adrita Karim (20146047), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This review does not involve any kind of trials on either animal or human models.

Abstract:

A global scientific initiative has been launched to produce viable vaccines against the SARS-CoV-2 virus in response to the COVID-19 pandemic. The review article offers a thorough investigation of few significant aspects related to COVID-19 vaccine, including its origin, epidemiology, historical background, dynamics of transmission, and evolution of mutant variants, shedding light on prevalent misconceptions and pathogenesis of the disease. An in-depth investigation of vaccine development pathways and mechanisms, which clarifies the scientific advances and parts of the immunization process, is the main theme of our analysis. In addition, we assess the significant influence immunization programs have on public health, going over the achievements, limitations. Through combining diverse perspectives, this project aims to offer a comprehensive understanding of COVID-19 vaccination's crucial role in battling the pandemic and shaping the curve of global health.

Keywords: SARS-CoV-2 virus; COVID-19 pandemic; Mutation variants; Pathogenesis; Vaccine development; Impact of vaccination.

Dedication

This project is dedicated to my beloved parents, who have provided me with unwavering support and encouragement throughout my life. As well as, to my late grandfather, whose wisdom and guidance still inspires me.

Acknowledgement

I can’t express enough gratitude to my supervisor, Mehedi Islam, Lecturer of the School of Pharmacy, Brac University, for his guidance, encouragement, and patience throughout this project. His expertise and guidance played a significant role in the formation and completion of this project. Moreover, I am grateful, as Sir has been most understanding and helpful throughout this project.

I would also like to thank our Honorable Dean Chairperson, Dr. Eva Rahman Kabir, School of Pharmacy, Brac University, for her cooperation and support during the project. In addition, I would like to thank our Deputy Chairperson, Dr. Hasina Yasmin, for her support.

I am also grateful to the faculty members in the Department of Pharmacy for their constant guidance throughout my academic years at Brac University. Lastly, I would like to thank my friends and seniors for helping me throughout my entire journey at the University.

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List of Acronyms

ACE2- Angiotensin Converting Enzyme 2

ADE- Antibody Dependent Enhancement

ARDS- Acute Respiratory Distress Syndrome

DAD- Diffuse Alveolar Damage

DMV - Double Membrane Vesicles

DPP4- Dipeptidyl Peptidase 4

EMA- European Medicines Agency

FDA- Food and Drug Administration

HIV- Human Immunodeficiency Virus

ICTV- International Committee on Taxonomy of viruses

MERS-CoV- Middle East Respiratory Syndrome Coronavirus

MHC- Major Histocompatibility Complex

RAPA- Rat Prostrate Adenocarcinoma

RTC- Replication Transcription Complex

SARS-CoV-2- Severe Acute Respiratory Syndrome Coronavirus-2

TMPRSS2- Transmembrane Serine Protease 2

TNF- Tumor Necrosis Factor

VEGF- Vascular Endothelial Growth Factor

Chapter 1

Introduction

Coronavirus disease which holds one of the highest numbers of human deaths causing a global pandemic and affecting every aspect of human lives has created a spark of interest in everyone. It is a deadly infectious respiratory disease, which is caused by a highly potent virus named, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Feng *et al.*, 2020). It was originated from a wet market named Chinese Huanan Seafood Market, where livestock animals are sold situated in Hubei province, China (Chan *et al.*, 2020). Moreover, on January 7,2020, Chinese researchers reported a new virus as a member of beta-CoV group or 2019 novel coronavirus (Heinz and Stiasny, 2021). Furthermore, by January 12, 2020 WHO officially named the virus 2019-nCoV and on February 11,2020 ICTV named the disease, COVID-19 (Belouzard, Chu and Whittaker, 2009) (Xu *et al.*, 2004). Additionally, after receiving reports of 2700 deaths and 80000 confirmed cases, the World Health Organization declared this situation as a global health emergency (Yuen *et al.*, 2020). Furthermore, there was rapid increase of the infected people led to WHO declare Coronavirus disease a pandemic by March 11, 2020. In addition, this new novel coronavirus contains an unseen novel strain which hasn't been seen yet in humans, creating huge anxiety among people around the world. However, the main issue that led to the pandemic is not only its fast transmission rate but its wide spectrum of clinical symptoms which vary patient to patient. To elaborate, some patients remained asymptomatic where others had severe viral pneumonia that led to respiratory failure, some had multi organ dysfunctions leading to sepsis and septic, and eventually death (Zaim *et al.*, 2020). This high fatality rate (2.9%) indicates high transmission ability of SARS-CoV-2 from genetic reassortment, which is much higher than SARS-CoV. In addition, genetic recombination of S protein in the receptor binding domain section also has a vital role in it. According to WHO, by April 2, 2020, globally 1016128 cases were reported, that included

245,175 cases and 6059 deaths from USA, 115242 cases and 13915 deaths from Italy, 112065 cases and 10348 deaths from Spain, 84789 cases and 1109 deaths from Germany, 81620 cases and 3322 deaths from China, 58441 cases and 5380 deaths from France, 50468 cases and 3160 deaths from Iran, 33718 cases and 2921 deaths from UK and rest from other countries (WHO, 2020).To lessen the COVID-19 morbidity and death toll and improve the falling economy there were a few mitigation strategies taken before the vaccine development (Zhao *et al.,* 2023). Which included compulsory wearing mask, washing hand, social and physical distancing, preventing social and crowd formation, lock downs, border closure, travel restriction and testing, quarantine and isolation (Anderson *et al.,* 2020; Bruinen de Bruin *et al.,* 2020). However, rather than using the strategies alone it is proven to give greater effect if used in combination (Bruinen de Bruin *et al.,* 2020). It was also predicted that more lives would have been saved if lockdown had been implemented early in the broadcast. The United Kingdom's short-term lockdowns, sometimes known as "circuit breaker intervention," were found to be most effective when the infection rate was low (Davies *et al.,* 2021). While fighting against Covid-19 Pandemic, one of the most promising weapons to save human life was the development of Vaccines. After the development of various vaccines, "World Health Organization" approved a number of vaccines. Some approved vaccines are: Pfizer BioNTech vaccine, Janssen Johnson & Johnson vaccine, Sinovac vaccine, Sinopharm vaccine, Oxford/AstraZeneca COVID-19 vaccine, Novavax vaccine, Moderna COVID-19 vaccine (*WHO*, 2020). As COVID-19 is new to mankind, controlling the pandemic and returning to the normal situation is dire wish for everyone. Therefore, to minimize this toll of death that caused a global pandemic due to this deadly virus, effective vaccines were much anticipated. In this review we want to highlight the multifactorial sides of Covid-19 vaccines, including their development, efficacy, safety, distribution, side effects, and prospective.

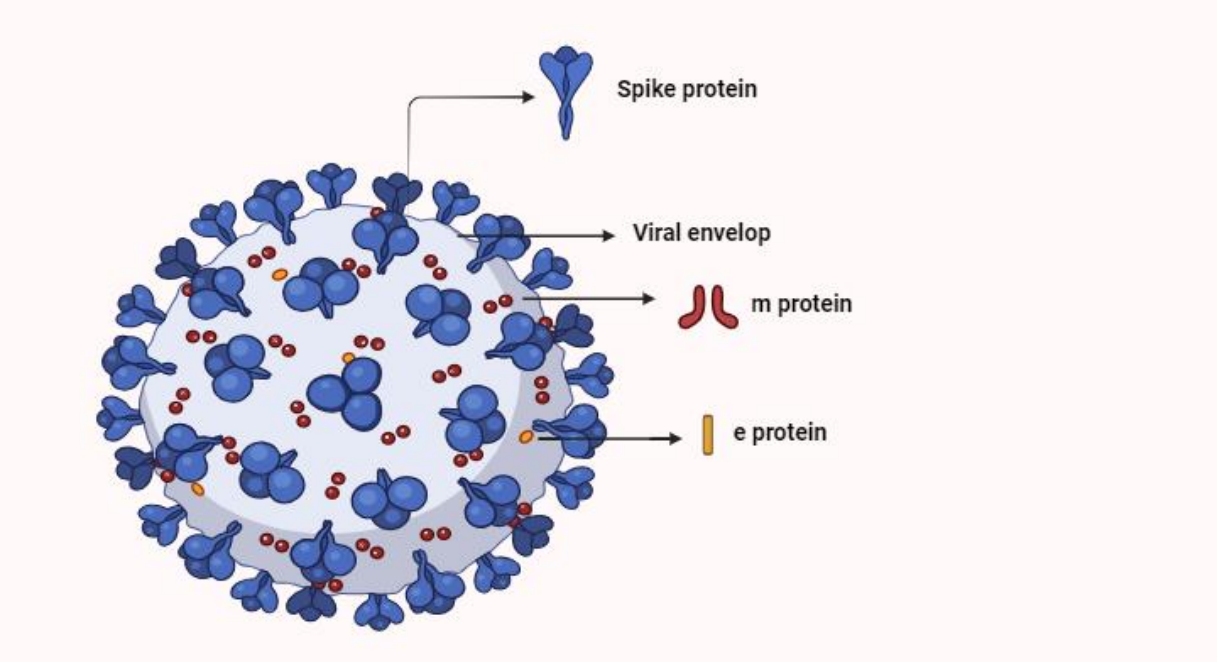

Figure 1: 3D structure of SARS-CoV-2 virus (Anderson *et al.*, 2020).

1.1. SARS-CoV-2; The Mysterious Entity Responsible for a Worldwide Crisis:

SARS-CoV-2 structurally belong to the beta coronavirus group containing Cov-229E and CoV-HKU1 pathogen, having a genome of 30 kb positive sense single strand RNA. In addition, this virus is enveloped in 14 open reading frames which in turn translated to polyproteins and produces nonstructural proteins. These nonstructural proteins can form double membrane vesicles DMV) that acts as a central hub for the genome replication, with the help of the RTC (Arya *et al.*, 2021). In addition, SARS-CoV-2 uses C-terminal domain in order to bind their receptors (Li et al., 2005).

Furthermore, about 1/3rd of the genome encodes the virus's structural proteins, while the remainder is used for expression and replication. These viruses include spike proteins (S), membrane glycoproteins (M), nucleocapsid proteins (N), envelope proteins (E) and hemagglutinin ester dimer proteins (HE) (Shereen et al., 2020). Furthermore, vaccinations target the S-protein which is a glycoprotein produced on the virus surface, which is responsible for both receptor interaction and fusion with the cell membrane. The SARS-CoV-2 virus's

major receptor in humans is ACE2, which is found in kidney, intestine, lung, heart and gallbladder cells and is recognized by the virus's S protein. After the ACE2 receptor and S protein binding, the proteolytic breakdown occurs thus incorporate with the membrane and it results in the viral RNA release into the cytosol (Fathizadeh *et al.*, 2021). The primary mechanism via which ACE2 lowers blood pressure is by converting the angiotensin II receptor to angiotensin I–VII. Another interesting finding is that, due to the variation in the S protein's genomic sequence, the binding affinity between ACE2 and SARS-CoV-2 is approximately 10-20 times higher than that between ACE2 and SARS-CoV (Fathizadeh et al., 2021).

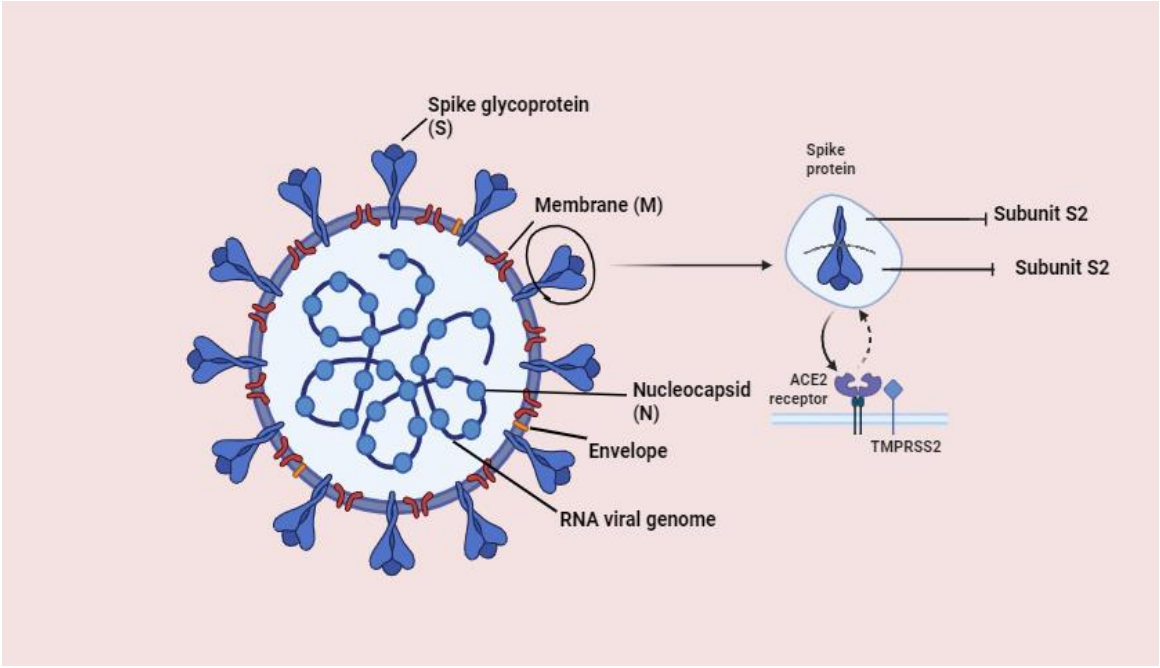

*Figure 2: Detailed structure of SARS-CoV-2 (*Xu *et al.*, 2020*).*

Chapter 2

Diving into the History of COVID-19

Under electronic microscope coronavirus are RNA virus that are enveloped positive sense single stranded viruses, which are 60 to 140 mm in diameter and 26 to 32 kbs in length. Another characteristic of them is they have spikes that have resemblance to the crown shape under the electron microscope (Aitken, 2010). Coronavirus has mainly these subgroups; alpha, beta, gamma and delta coronavirus. Up until 2002, before the epidemic outbreak in Guangdong, China, it was considered as a transmitted disease by animals. That epidemic outbreak is proof that SARS-CoV are zoonotic and present in humans and animals causing severe infection in gastrointestinal, hepatic, neurological system and most importantly respiratory system (Yin and Wunderink, 2017). Additionally, by 2002 and "03 beta genera with the starting point caused SARS that led the bats as reservoirs and humans as transmitter through the palm civet cats as host giving a 11% fatality rate. Similarly, in 2012, bats as reservoirs and camels as hosts transmitted to humans leading to an endemic in middle eastern countries with a fatality rate of 34%. This was identified as MERS-CoV (Menachery *et al.*, 2013). Furthermore, another epidemic originated from a seafood market in China in December 2019, which was a transportation hub for unconventional live animals. Upon further research and sequence-based analysis from samples, the virus was identified and showed around more than 95% similarity with bat CoV and more than 70% similarity with SARS-CoV (Grifoni *et al.*, 2022). Upon further investigation it was known that this virus was transmitted by human-to-human contact around the world. Namely, exposure to the virus via close contact with the affected person, coughing, sneezing, respiratory droplets that can penetrate lungs via breathing. Undoubtedly, I urge readers to consider the broader implications of our findings as we delve deeper into the details of the COVID-19 epidemic.

2.1 An Overview of the COVID-19 Pandemic:

COVID-19, a pressing global crisis, documented first in China, specifically in Wuhan province in December 2019. It was reported that around 571 cases of COVID-19 by January 22nd in altogether 25 provinces in China. Alarmingly, these case numbers grew to 7734 by January 30th and other countries, reported 90 cases of COVID-19 (Rothan and Byrareddy, 2020). The first wave of COVID-19 had mortality rates about 110574 cases and 13,155 death tolls by April 1st in Italy (Boccia, Ricciardi and Ioannidis, 2020). However, SARS-CoV-2 infected individuals are the primary source of virus transmission due to the large number of viruses produced in the upper respiratory tract prior to symptoms appearing (Zou *et al.*, 2020). Furthermore, people of all ages are vulnerable to this deadly virus not just a special group which is alarming, however, people who are older or have certain pre-existing medical issues are more vulnerable to serious illness (van Doremalen *et al.*, 2020). This virus is transmitted through coughing and sneezing, producing large infected droplets by symptomatic patients, having ability to spread about 1-2 m and importantly can deposit on unalive surfaces from asymptomatic inhibition prior leading to symptoms. Which can be further solidify by the study of virus mode of transmission, where it was reported that 89% transmission takes place due to close human contact in family, 33% in the epidemic locale contact and 22% cases have both exposures. To elaborate, this COVID-19 outburst taken place during Spring Carnival in China, where approximately 3 billion people travel countrywide. Additionally, this serves as a favorable condition for the transmission of this contagious disease and proven to add difficulties in control and prevention of the epidemic (Liu *et al.*, 2020). Moreover, an interesting characteristic of the virus is that in their favorable condition they can stay viable on surfaces for days but not in the presence of disinfectants. Such as, sodium hypochlorite, hydrogen peroxide etc. The infection can be caused through many routes such as through breathing, touching contaminated surfaces and then touching the nose, mouth and eyes with

the contaminated hand (Liu *et al.*, 2020) (Cheng and Shan, 2019). SARS-CoV-2 primarily affects men, resulting in notable increases in age-related mortality among elderly individuals who are already fragile. Meanwhile, the four coronaviruses that do not disturb society primarily affect women and children aged five to fourteen (Movert *et al.*, 2013).

Another factor complicating case epidemiological surveillance is the highly mutation-causing nature of coronaviruses, leading to inaccurate interpretations of comparative evolution (Lv *et al.*, 2020). The idea that COVID-19 sequences were comparable to HIV led to rumors that COVID-19 was a bioweapon that had been manufactured. However, it was proved that they are similar to the sequence in HIV-1 gp 120 and a cellular receptor recognition protein Gag (Zhou *et al.*, 2020). However, they are inserts that appear in protein's hyper variable regions and has a short length about 6 residues which leads to the conclusion of it occurring naturally. Therefore, there were no proof to support that COVID-19 is man made and have similarity between MERS-CoV (51.8%) and SARS-CoV-1 (79%) with previous two Coronaviruses and originated from bats (Fan *et al.*, 2019; Ren *et al.*, 2020). To solidify the statement, SARS-CoV-2 has 96% similarity with sequence of wild random sampling (Zhou *et al.*, 2020).

Chapter 3

Exploring the Fascinating Pathogenesis of COVID-19

A key component in the viral entrance process in the host cell is the S protein cell of the coronavirus (De Wit *et al.*, 2016). SARS-CoV-2 and SARS-CoV both use the ACE2 receptor, whereas SARS-CoV and MERS-CoV use the DPP4 and CD209L receptors respectively. Additionally, MERS-CoV needs the two step furin activation for membrane fusion (Millet and Whittaker, 2014). Clathrin dependent and independent endocytosis mediated entry is another way for the SARS-CoV virus (Li *et al.*, 2003). Viral replication is started when the viral RNA genome is translated to structural proteins and polyproteins upon entrance (Perlman and Netland, 2009). While cathepsin L helps entry via endolysosomes. TMPRSS2, which is expressed in a variety of organs, primes the Spike protein and promotes viral entry (Antalis, Bugge and Wu, 2011). The main site of entry for SARS-CoV-2 is ACE2, which is widely expressed in organs like the lung (Tian *et al.*, 2020). This causes pathological alterations such disseminated intravascular coagulation and extensive alveolar destruction. Most of them were consistent with diffuse alveolar damage (DAD). (Tian *et al.*, 2020). Findings of the clinical studies showed that causes of patient death were caused by CD4+ mononuclear cell accumulation as well as locally activated megakaryocytes in lung, deposition of fibrin, formation of clot and platelet aggregation (Autopsias., 2020).

ARDS symptoms and bilateral diffuse alveolar destruction with cellular fibromyxoid exudates are noticed in pathological studies from severe COVID-19 cases (Le *et al.*, 2020). Histological analysis indicates alterations that are similar to those associated with viral cytopathic illness, such as interstitial mononuclear inflammatory infiltration and multinucleated syncytial cells that resemble SARS and MERS patients (Ding *et al.*, 2003). Microvascular steatosis along with minor cardiac tissue inflammation are seen in liver biopsies, which may indicate a limited direct

cardiac impact (Le *et al*., 2020). Those that die have a lot of mucus secreted in their lungs, which sets them apart from SARS and MERS. These results draw attention to the unique pathological characteristics of severe COVID-19 and its possible effects on different organ systems (Contreras., 2020).

3.1 Cytokine Storm:

According to clinical investigations, lung inflammation caused by SARS-CoV-2 infection can become lethal due to uncontrollably high inflammatory responses. Furthermore, SARS-CoV-2 induces ADE, ACE2 downregulation, and shedding in addition to fast viral multiplication and cellular damage (Fu, Cheng and Wu, 2020). As mentioned earlier SARS-CoV-2 has the similar introduction receptor (ACE2), like SARS-CoV which points the similarity between them in terms of kinds of infected cells and targets (Gu *et al.*, 2005). In addition, onset of the viral replication causes endothelial and epithelial cell death and vascular proliferation leading to excessive production of chemokines and pro-inflammatory cytokines. Furthermore, acute lung damage results in the loss of ACE2 function of the lung because ACE2 downregulation and shedding cause the renin-angiotensin system (RAS) to malfunction and increases inflammation and vascular permeability (Imai, Kuba and Penninger, 2008). Similar to SARS-CoV, SARS-CoV-2 infected patients who develop early neutralizing antibodies, go through persistent inflammation, ARDS and even death, where most of the patients survive the inflammatory responses (Fu, Cheng and Wu, 2020). Additionally, ADE promotes absorption of the infectious viral antibody complexes by cells through their interaction with Fc receptor, Fcγ receptor that results in increased target cell infection (Takada and Kawaoka, 2003). In patient's lung, the interaction between the Fcγ receptor and the complex of anti-S protein neutralizing antibodies will promote inflammatory reactions along with long-term viral replication (Fu, Cheng and Wu, 2020).

3.2 Acute Respiratory Distress Syndrome:

The most common cause of severe mortality from respiratory illnesses and acute lung injury is acute respiratory distress syndrome (ARDS), a potentially fatal condition in which the lungs and blood circulation do not receive enough oxygen (Thompson, Chambers and Liu, 2017) Similar to SARS-CoV, MERS-CoV causes severe respiratory distress in individuals with fatal SARS-CoV-2 infections, requiring mechanical ventilation. Similar features were found in the histology (Ding *et al.*, 2003; Contreras, 2020). Furthermore, ARDS is connected to inflammatory cytokines and genetic vulnerability. Research has indicated that over 40 g4n4 candidates, including ACE2, VEGF, TNF, and interleukin 10 (IL-10), were associated with the outcome of ARDS. As a result of ARDS side effects, the plasma level of IL-6 and IL-8 is also elevated (Thompson, Chambers and Liu, 2017).

3.3 Immune Dysfunction:

Reduction and hyperactivation of CD4 T cells as well as CD8 T cells in severely affected population. CD4 T cells in high concentrations cause proinflammatory and CD8 T cells also cause cytotoxic granules. In addition, causes critical factors for severity such as systemic inflammation and tissue damage leading to mortality (Zhu *et al.*, 2020).

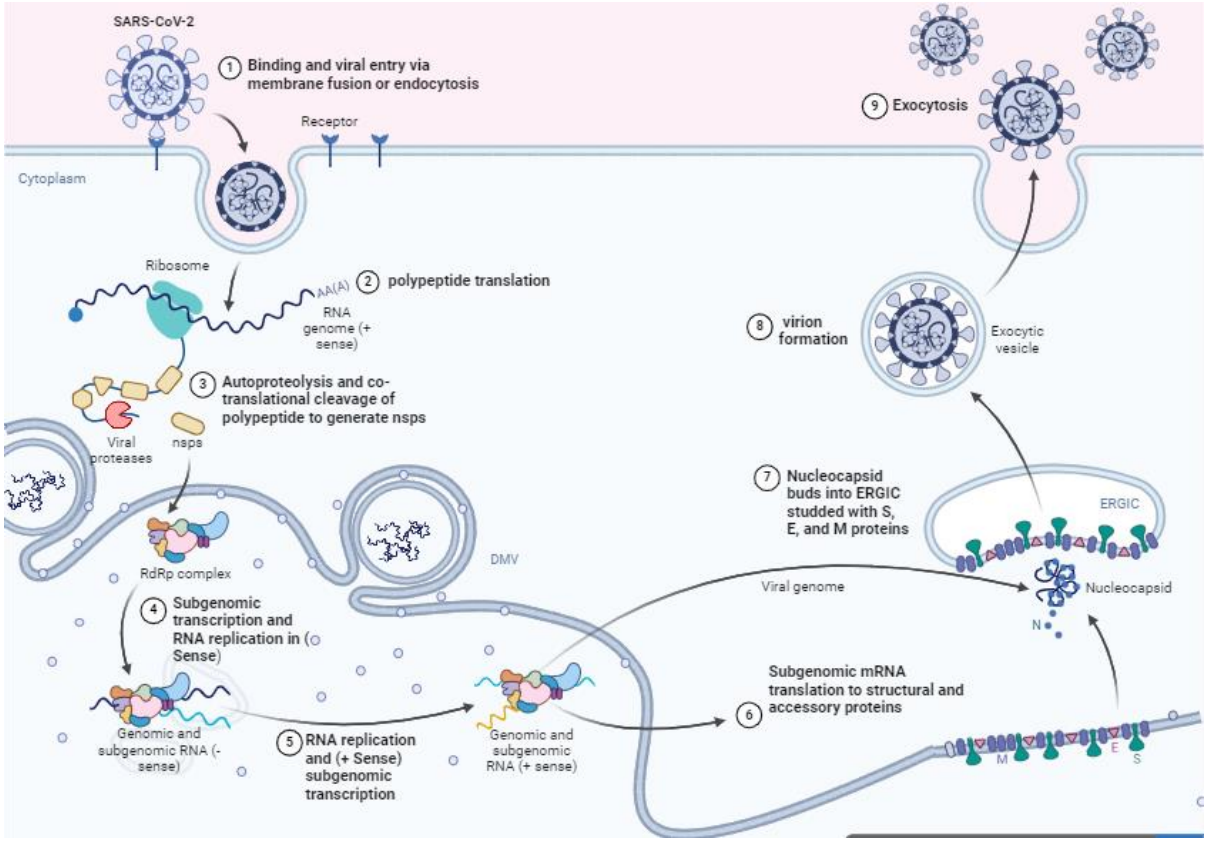

Figure 3: Infection cycle of the SARS-CoV-2 inside the host cell (Hartenian *et al.*, 2020).

Chapter 4

Navigating the Mutation Landscape of SARS-CoV-2 Variants:

Concerns over vaccine efficacy against novel variations such as Alpha, Delta, and Omicron have arisen due to the SARS-CoV-2 virus's evolution. It is because of this evolution that variant-specific vaccinations are being studied. Before reentering human populations, these variants, including Alpha, which expanded throughout the UK by the end of 2020, are expected to emerge from different hosts, such as domestic and wild animals. This emphasizes how crucial it is to maintain ongoing surveillance and develop vaccines in order to combat the evolving COVID-19 variant environment (Koelle *et al.*, 2022). The Delta variation, which originated in India (Dhar *et al.*, 2021) and showed stronger replication capability and transmissibility together with reduced sensitivity to host immune responses, came next to the Alpha version, which was recognized for its increased transmissibility and enhanced binding to ACE2 (Subbarao *et al.*, 2021). Despite these traits, research has demonstrated that the existing vaccinations are still effective against both types, and booster doses offer extra security in case immunity declines (Pormohammad *et al.*, 2021), (Tang *et al.*, 2021). The Omicron variation, which is marked by several spike glycoprotein alterations, presents a problem since it can infect people who have already been vaccinated and avoid being recognized by antibodies from past infections (Liu *et al.*, 2020). The efficiency of vaccines against Omicron has been variable; mRNA-1273 boosters have proven to be more effective than ChAdOx1 nCoV-19 boosters (Goel et al., 2021).Long-lasting protection against different variations can be provided by cellular immune responses, even though antibody levels may eventually decrease. It's important to remember, though, that estimates of vaccine effectiveness against severe disease may not match those against infections with symptoms(Andrews *et al.*, 2022).

Table 1: Analyzing SARS-CoV-2 Strain's Diversity and Effects.

Virus Subtype	Gene Mutation	Characteristics	Location of breakout	Date of Epidemic	Changes occur
SARS-CoV	Beta coronavirus subgroup 17.	Severe respiratory disease and high mortality rate.	Guangdong province, China.	2002-2003	Exhibits limited mutation than SARS-CoV-2.
MERS-CoV	Beta CoV subgroup.	Mild upper respiratory injury, severe upper respiratory injury, pneumonia, ARDS and renal failure 19.	Saudi Arabia and the Middle East.	2012	Not frequent mutation as SARS-CoV-2 but evades the human immune system efficiently.
SARS-CoV-2	Alpha variant	Increased transmission, potent immune evasion.	United Kingdom.	September 2020	Spike Protein mutation including N501Y and P681H. Enhancing the ability to bind to human cells and transmissibility.

SARS-CoV-2	Beta variant	Increased transmission ability and immune evasion.	South Africa.	May 2020	Spike Protein mutation inclusion N501Y, E484K and K417N.
SARS-CoV-2	Gamma variant	Increased transference ability and immune evasion.	Brazil	November 2020	Spike Protein mutation including N501Y, E484K and K417T.
SARS-CoV-2	Delta variant	Increased transmission ability and immune evasion.	India	December 2020	S-protein mutation along with L452R and P681R.
SARS-CoV-2	Omicron variant	High potential in transmission and immune evasion.	South Africa.	November 2021	Spike Protein mutation including T478K,N501Y and K417N.

Chapter 5

Features of Coronavirus for Vaccine Development

Developing vaccine for a novel virus that caused a global pandemic is undoubtedly hectic as most of the vaccines take a complex of 8 year to be available for the mass.

- However, most of the vaccine that have been approved by WHO for use in general people are for emergency use with conferred protection, safety and efficacy while monitoring selected population for clinical trials (Torres-Estrella *et al.*, 2022). Amid these, COVID-19 vaccine development was different in the sense that SARS-CoV-2 has around 79.5% genetic similarity to SARS-CoV (Rossi *et al.*, 2020).
- Prior knowledge from studies into the virus family and the application of modified mRNA technology, which was invented by Katalin Karikó, sped up the evolution of the COVID-19 vaccine (Karikó *et al.*, 2008).
- For the purpose of developing the COVID-19 vaccine, a variety of technology platforms were assessed; platforms based on DNA or mRNA showed promise for quick antigen alteration (Karikó *et al.*, 2008).
- The pace of development can be seen in the vaccines like mRNA-1273 (Moderna), which entered clinical testing not long after the sequence was identified (Karikó *et al.*, 2008).
- Vaccines based on viral vectors demonstrated potential as well, exhibiting robust immune responses along with increased protein expression and stability (Torres-Estrella *et al.*, 2022).
- In order to increase immunogenicity and allow for the use of lesser dosages, adjuvants were used. This allowed for a greater vaccination coverage without sacrificing protection.

- Making the viral spike (S) protein target, the specific SARS-CoV-2 antigens used in vaccine development sought to elicit neutralizing antibodies against it (Ren *et al.*, 2020).
- However, it is unclear how this many S protein variations utilized in vaccinations relate to the genetic epidemiology of the illness (Ren *et al.*, 2020).

5.1. Various Vaccine Platform:

In response to the COVID-19 outbreak, immediate action was required and vaccination campaigns and other mitigating measures were essential in reducing the virus's virulence (Krammer, 2021). In order to stop virus transmission, effective vaccines must stimulate humoral and cell-mediated immune responses. Governments, academic institutions, and pharmaceutical firms have collaborated globally to facilitate the development and production of vaccines (Chavda *et al.*, 2022). Safety and effectiveness of vaccines were guaranteed by thousands of participants in clinical trials. Vaccines work by stimulating immunity using viral antigens; vaccines utilizing viral vectors work by activating machinery within the host to produce antigens. This has allowed for their quick dissemination while keeping an eye on side effects and safety (Krammer, 2021). Inactivated virus, recombinant viral vectors, virus-like particles, protein subunit, and nucleic acid-based vectors are some pathways of vaccines approved by the WHO (*Timeline: WHO's COVID-19 response*, 2021; *COVID-19 vaccine tracker and landscape*, 2023).

Table 2: Different Vaccine Candidates, their Characteristics and Platform.

Vaccine platform	**Used SARS-CoV-2 antigen**	**Response via neutralizing antibody**	**Existing anti vector immunity**	**Route of administration**	**Overall immunity**	**Example**
Ad5 (human serotype 5 adenovirus)	S protein	Existing anti vector immunity can affect the quality and duration.	High prevalence in blood and lower in respiratory lung.	Parenteral intramuscular route.	Usually strong with single dose administration.	Ad5-nCoV.
Ad26 (human serotype 26 adenovirus)	S protein	Existing anti vector immunity can affect the quality and duration	Medium prevalence.	Parenteral intramuscular route.	Weaker and requires continuous boost vaccination.	Ad26.COV2-S
ChAd (chimpanzee adenovirus)	S protein	Not hindered if lacked existing anti vector immunity	Very poor prevalence.	Parenteral intramuscular route.	Much stronger even in single delivery.	ChAd Ox1 nCov-19.

VSV (vesicular stomatitis virus)	S protein	Not hindered if lacked existing anti vector immunity	None.	Parenteral intramuscular route.	Passable with single delivery.	COVID-19 vaccine.
mRNA vaccine	S protein or RBD	Not hindered if lacked existing anti vector immunity	None	Parenteral intramuscular route.	Gives good action in continuous delivery.	mRNA-1273, bnt162b.
DNA vaccine	S protein	Not hindered if lacked existing anti vector immunity	None	Parenteral intramuscular route.	Requires continuous delivery and weaker than mRNA vaccine.	ZyCov-D, GX-19.
Protein Subunit vaccine	S protein/ RBD	Strong origination.	None.	Parenteral intramuscular route.	Weak immunity requiring continuous vaccination.	NVX-CoV237.

Virus like particle	Multiple viral antigen.	Strong origination.	None.	Parenteral intramuscular or respiratory mucosal route.	Weak immunity requires continuous vaccination.	COVID-19 vaccine.

5.1.1 Viral Vectored Vaccine:

For large production, adenovirus vectored vaccines take advantage of efficiently transduced genes and stable biology (Crystal, 2014). Humans and other animals, such as chimpanzees, can be isolated from these vectors (Ewer *et al.*, 2017). The 36 kb genomes of widely used human adenoviruses, such as Ad5 and Ad26, are constructed with inverted terminal repeats that function as self-primers (Daussy, Pied and Wodrich, 2021). Early (E1–E4) and late transcripts from the virus encode structural and non-structural proteins, respectively. Vaccines containing the coronavirus S protein, which is necessary for viral entrance, can be given as viral vector or DNA recombinant vaccines (Ong *et al.*, 2020). Importantly, a transgenic cassette must be inserted into adenoviral backbones by direct cloning or homologous recombination. Robust expression is sustained by strong promoters in the cassette (Afkhami, Yao and Xing, 2016). The S protein is broken down by host proteases into the S1 subunit and S2 subunit, where S1 binds to the ACE2 and S2 promotes viral entry and membrane fusion. In order for vaccine-

induced immunity to occur, adhesins such as the S protein are critical for, viral attachment to host genomes (Chavda *et al.*, 2021). Technologies that improve adenovirus production, such as AdEasy and RAPA cell lines, are essential for vaccine efficacy (Ong *et al.*, 2020).

5.1.2 mRNA Vaccine:

mRNA-based vaccines (mRNA-1273) encode S 2P antigen that consist SARS-CoV2 glycoprotein along with transmembrane anchor. In addition, it further interacts with S1-S2 cleavage site. Moreover, the S 2P antigen perfusion conformation is stable with the assist of two proline substitute at position 986 and 987 of amino acid, which is on the top of S2 subunit's central helix (Hwang *et al.*, 2020).

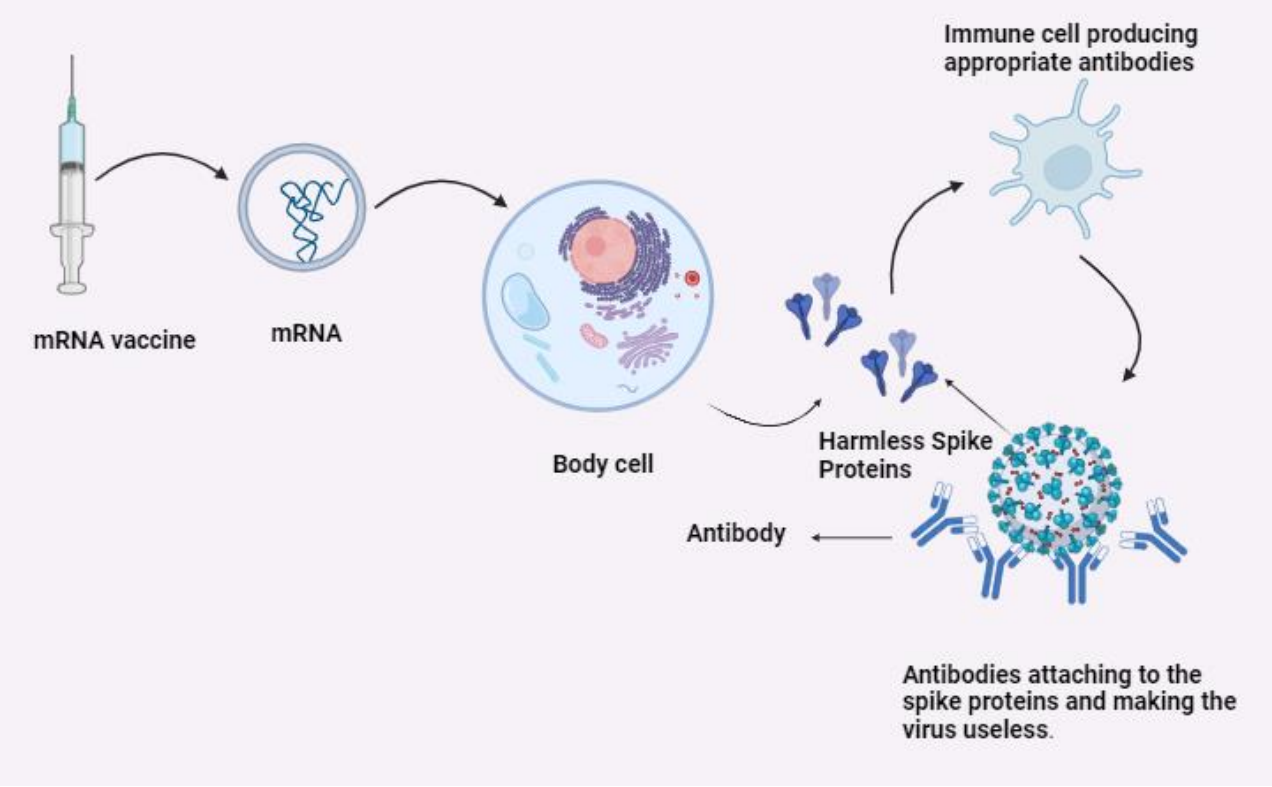

Figure 4: mRNA vaccine's mechanism of action (Cox and Brokstad, 2020).

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5.1.3 Protein Subunit Vaccine:

Purified proteins or protein fragments from the virus, such as the S protein of SARS-CoV-2, are included in protein subunit vaccines. Recombinant DNA technology or other biotechnological techniques are used to create these proteins. The proteins boost the body's immune system, which includes producing antibodies, when they are supplied. subunit vaccinations that only include a portion of the S protein; occasionally, they also include pieces of other viral proteins (Chavda *et al.*, 2021).

5.1.4 Inactivated or Attenuated Viral Vaccines:

Through alteration or removal of virulence genes, virus strains are attenuated in this process, which in turn will provide limited ability of replication in host cell thus losing the ability to initiate disease in the body. Therefore, following this step for coronavirus, deleting some non-structural protein or structural protein like E protein that are not important for replication process leads to the reduction in strength and production of a great strain of the vaccine (Hou *et al.*, 2019). However, the reversing attenuated phenotype is a serious issue. Therefore, a gene named 2'-O-methylase of the SARS-CoV genome will give improved antiviral response like hiding its RNA from IFIH1 and IFIT1, its host cell protein. (Menachery *et al.*, 2014). In addition, codon deoptimization approach containing modification of nucleic acid sequence leads the usage of codons for encoding wild type amino acid sequence that reduces the translation time of the viral protein (Mueller *et al.*, 2020). However, these types of vaccines are less stable and safe in the immunization process, making them less suitable for immunocompromised patients. In addition, as the attenuated strain is unable to reverse genetically, thus cannot convert into pathogen, turning coronavirus to vaccine, which is naturally known to recombine (Tao *et al.*, 2017).

Chapter 6

The Dynamic SARS-CoV-2 Vaccine Landscape; Types and Technologies:

Table 3: Overview of the COVID-19 Vaccine.

Vaccine type	Vaccine Name	Developer Name	Antigen Used	Storage Term	Dosing Plan	Date of approval	Efficacy
mRNA	Comirnaty	Pfizer Inc. BioNTech SE	Full length spike protein.	Stored at ultra cold storage (-70°C)	Requires 2 doses between 21 days.	11 December, 2020 for emergency use and approved date is in August 2021.	Effective 95% for disease and 87.5% for severe disease situations.

mRNA	Spikevax	Moderna, Inc.	Full length spike protein.	Stored at (-20°C)	Requires 2 doses 28 days apart.	18 December, 2020. Approved on January 2022.	Effective 94% for disease and 100% for severe disease conditions.
Viral vector	Astra-Zeneca-Oxford	AstraZeneca in collaboration with the University of Oxford.	Spike Protein.	Stored at 2-8°C.	Requires 2 doses 12 weeks apart.	30 December, 2020	Effective 70% overall. 64% after 1st and 70.4% after 2nd dose.
Viral vector	Janssen Johnson & Johnson	Janssen Pharmaceuticals Companies of	Spike Protein.	Stored at 2-8°C.	Requires only 1 dose	27 February, 2021.	Data varies in geographical position

		Johnson & Johnson.					such as 72% in the USA, 57% in South Africa.
Protein subunit	Nuvaxovid	Novavax, Inc.	Recombinant full length and perfusion 5 protein.	Stored at 2-8°C.	Requires 2 doses between 4-12 weeks.	Not yet.	89.7% effective in the UK and 60% effective in South Africa.
Inactivated virus	Sinovac	Sinovac Biotech Ltd.	Inactivated strain of virus which is created from vero cells.	Stored at 2-8°C.	Requires 2 doses between 14 days.	Not yet.	65% effective for severe conditions prevention.

Inactivated virus	Sinopharm	China National Pharmaceutical Group Corporation (Sinopharm)	Cultured and inactivated variant of SARS-CoV-2 virus.	Stored at 2-8°C.	Requires 2 doses between 3 to 4 weeks.	Not yet (only for emergency use)	Effective 50%-80%

6.1 mRNA-Based Vaccine's Mechanism of Action:

6.1.1 Pfizer - BioNTech (BNT 162b2):

For stability, the mRNA encoding the spike protein is encased in lipid nanoparticles and injected intramuscularly (Kumar *et al.*, 2020). After the mRNA is introduced into the host cells, ribosomes convert it into spike proteins. By presenting these proteins on the cell membrane through MHC-1 and MHC-2 molecules, T helper cells are activated (Cox and Brokstad, 2020). B-cell development into plasma cells, which generate spike protein-specific antibodies, is stimulated by activated T helper cells. For sustained immunization, memory T cells are also generated. By using MHC-1 to identify spike protein fragments, T cytotoxic cells cause apoptosis in infected cells to stop the virus's propagation (He *et al.*, 2021).

6.1.2 Moderna (mRNA-1273):

Using mRNA encoding the spike protein to initiate an immune response, the Moderna COVID-19 vaccine (mRNA-1273) functions similarly to the Pfizer-BioNTech vaccine. For optimal stability and distribution, the mRNA is encapsulated in lipid nanoparticles. Production of antibodies, memory T cell activation, and possibly T-cytotoxic cell removal of infected cells are all components of the coordinated immune response (Cox and Brokstad, 2020).

6.2 Viral Vectored Based Vaccine's Mechanism of Action:

6.2.1 AstraZeneca:

A modified chimpanzee adenovirus is used as a viral vector in the AstraZeneca COVID-19 vaccine, which uses a novel technique to deliver genetic material. The probability of pre-existing immunity is reduced by this adenovirus, which has never been met by human populations before. A viral protein resembling the S-peptide of the SARS-CoV-2 virus is encoded in the vaccine's modified DNA vector (Daussy, Pied and Wodrich, 2021). After being administered the chimpanzee adenovirus attaches itself to human cells by releasing its DNA into the cytoplasm before moving on to the nucleus. Significantly the host enzymes convert the viral DNA into mRNA rather than integrating it into cellular DNA. The viral proteins, such as, S peptide is subsequently produced by this mRNA by interacting with host cell ribosomes in the cytoplasm. T-cells, B-cells, and plasma cells are activated when expressed proteins are displayed on the cell membranes as MHC-I and MHC-II complexes. The development of antibodies, especially those directed against the S-peptide, is a result of this coordinated immunological response, which enhances the vaccine's ability to elicit protection against COVID-19 disease (Chavda *et al.*, 2021).

6.2.2 Janssen (Johnson & Johnson):

Adenovirus 26 CoV2 strain is used in the Johnson & Johnson created Janssen COVID-19 vaccine to transfer genetic material that code for the SARS-CoV-2 spike protein or S protein. These genetic instructions for the spike protein are carried by this benign cold virus, which serves as a vector (Patel *et al.*, 2022). The adenovirus vector, which was designed to stop replication in human cells, inserts its DNA into the nucleus without joining forces with the DNA of the host cell. Human cells use the mRNA to make spike proteins once they are inside. Strong immunological responses are triggered because they are required for defense against the infection of SARS-CoV-2 and involve B-cells, cytotoxic cells, plasma cells, CD4 and CD8 T-cells, and interleukins. These reactions produce T cells and antibodies, which offer protection against free virus particles and infected cells. The immunological response triggered by the Janssen vaccination aims to prevent COVID-19 infection (Grifoni *et al.*, 2020).

6.2.3 Sputnik V:

The Sputnik V, a COVID-19 vaccine follows a procedure similar to that of vaccines produced by Johnson & Johnson and AstraZeneca. It uses adenovirus vectors that have been altered to contain DNA fragments that have been designed to encode the SARS-CoV-2 virus' S protein. Administered, the adenovirus causes infection in cells, causing them to replicate the coronavirus spike protein according to genetic instructions. The immune system is activated by the presence of this protein, which results in the generation of T cells and antibodies. Notably, in order to ensure safety, the viral vectors utilized are engineered to be incapable of replicating in human cells. By administering two doses of distinct adenovirus strains, the regimen seeks to improve the immune response's longevity and efficacy, shielding recipients from further SARS-CoV-2 infections (Jones and Roy, 2021).

6.3 Whole Virus-Based Vaccine's Mechanism of Action:

6.3.1 Sinovac/CoronaVac:

The COVID-19 vaccine Sinovac, also referred to as CoronaVac, was created in China and Brazil using an inactivated virus as the antigen. This kind of vaccine works by utilizing a frail or inactivated version of the virus, which still has the ability to stimulate the immune system but is unable to cause illness. A number of nations, including Indonesia, Turkey, and Singapore, have administered the CoronaVac vaccine (Halim, 2021). Its effectiveness against mild or moderate types of the disease has been estimated by preliminary research to be around 78%. This shows that the vaccination works to stop COVID-19 symptoms from occurring, making it an important tool in the global fight to stop the SARS-CoV-2 virus spread. In the context of the COVID-19 pandemic, CoronaVac serves as an illustration of the long history of vaccine development using inactivated or weakened virus technology (Halim, 2021).

6.3.2 Sinopharm:

Sinopharm, an adjuvant-containing inactivated vaccine, is frequently administered to pregnant women along with numerous other vaccines that have a well-established safety profile. Sinopharm is developed by Beijing Institute of Biological Products Co, China. It uses the whole inactivated virus as the medium precisely, Wuhan-Hu-1 like HB02 as virus strain.(Heinz *et al.*, 2021) It is known as, BBIBP-CorV or Sinopharm COVID-19 vaccine. However, there is no stabilizing mutations recorded. The eukaryotic production cell line is called Vero, certified by WHO for vaccine production, in this case. Furthermore, a large multi-country Phase III trial found that two doses, given at a 21-day interval, demonstrated a 79% efficacy against symptomatic SARS-CoV-2 infection 14 days or more after the second treatment. 79% of vaccines were effective in preventing hospitalization (Xia *et al.*, 2021).

6.4 Protein Subunit Vaccine's Mechanism of Action:

6.4.1 Novavax:

The US-developed COVID-19 vaccine NVX-CoV2373 uses protein components that resemble the spike protein of SARS-CoV-2. Adults show strong humoral and cellular immunological responses, pending approval by the European Medicines Agency (Heath *et al.*, 2021). Regulatory agencies' rolling review process speeds up the review process and enables real-time assessment of changing data. This strategy bolsters the collection of vaccines against the pandemic by utilizing innocuous viral components to stimulate potent immune responses against COVID-19 (*Novavax.*, 2021)

Chapter 7

Health Impacts of COVID-19 Immunization:

Vaccination against COVID-19 has been demonstrated to substantially lower the risk of hospitalization, serious illness, and death from the causative virus. For those who may be more susceptible to the disease's consequences, immunization offers vital protection by enhancing the immune system ability to identify as well as combat the causative virus. Additionally, Immunization slows the virus's spread throughout communities in addition to protecting those who receive it (WHO, 2020). Immunization helps keep outbreaks under control and stops the virus from spreading to more vulnerable groups by reducing the overall prevalence of COVID-19. Furthermore, COVID-19 can lead to some long-term health consequences, which is referred as long COVID. This includes lasting signs including exhaustion, dyspnea, and mental challenges. Vaccination can help prevent these long-term health effects by reducing the risk of infection and subsequent complications. Also, pandemic-related stress and anxiety can be reduced by the accessibility of potent vaccinations and the possibility of developing herd immunity through immunization campaigns. Improving mental health and general wellbeing, vaccination offers hope for a return to normalcy. Finally, immunization against COVID-19 is essential for society to reopen and resume social contacts, economic activity, and educational opportunities. Campaigns for vaccinations help public health regulations and limits to be loosened, allowing people to gradually resume their pre-pandemic lifestyles.

7.1 COVID-19 vaccination program; positive or negative:

Mass immunization programs has proven beneficial in avoiding disease, hospitalization, and mortality from the COVID-19 pandemic. Additionally, contributing primarily favorable response that is seen worldwide. Furthermore, reviving economies and easing public health

regulations enabled countries with high vaccination rates to stop the virus spread and safeguard vulnerable populations and providing the hope for a return to normalcy.

- **Positive Impact:**

  The world health community has shown its capacity to mobilize resources and successfully respond to emerging infectious illnesses through its unprecedented collaboration in the evolution, production, and distribution of COVID-19 vaccines (Torres-Estrella *et al.*, 2022). Countries can considerably stop the virus from spreading throughout their communities and safeguard susceptible groups by attaining high vaccination rates. Recognized as a crucial instrument in stemming the pandemic, vaccination offers promise for a return to normalcy through lowering public health restrictions, reopening economies, and restarting social activities

- **Negative Impact:**

The global response to the pandemic has been mostly viewed as having progressed positively with the implementation of the COVID-19 immunization program. However, issues such as obstacles including vaccine distribution inequities, supply chain interruptions, and vaccine skepticism negatively impacted the situation. In addition, breakthrough infection due to the virus' mutation ability or variants having different transmission ability also creates a lack of protection even after the vaccination. Moreover, few common side effects such as, pain, fatigue, nausea, muscle pain, chills and some adverse reactions to the virus such as, anaphylaxis, myocarditis, blood clotting disorder, have been seen which led to skepticism about the vaccines (Lazarus *et al.*, 2023) (NHS, 2024).

Chapter 8

Conclusion:

Conclusively, exploring the complexities around COVID-19 vaccinations exposes an incredible voyage of scientific inventiveness, international cooperation, and unmatched perseverance amidst a catastrophic pandemic. A wide variety of vaccination platforms has been developed, each with specific advantages in inducing strong immune responses against SARS-CoV-2 virus. These include significant creation of mRNA vaccines as well as the use of viral vectors, protein components, and inactivated viruses. These vaccinations have shown exceptional success in lowering sickness, hospitalizations, and fatalities globally through rigorous scientific trials, authorizations for emergency use, and mass immunization programs. This is a key milestone in our combined efforts to battle COVID-19. To combat the virus's growing risks, however, constant monitoring and continued research are needed. These problems include vaccination reluctance, worldwide disparities in access, and the introduction of new variations. We must not compromise in our dedication to evidence-based policymaking, community involvement, and international cooperation as we negotiate the challenges of vaccine research and implementation. We can create a strong framework for pandemic preparedness in the future by utilizing the observations gained from the COVID-19 outbreak. This will guarantee that everyone can benefit from scientific advancements and that our determination will not falter in the face of difficulty. Working together and being determined are essential to securing a safer future. The COVID-19 vaccination has lessened the virus's impact, but equitable distribution and adverse effects still need to be addressed. It is essential to practice transparency, involve the community, and refute false information. To implement successful public health policies and close knowledge gaps, ongoing research is required.

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