A Review on Potential COVID-19 Vaccines

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis 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 thesis 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 thesis/project titled "A Review on Potential COVID-19 Vaccines" submitted by Md. Rashedul Islam (16346044) of Spring, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy (Hons.) on February 2021.

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Ethics Statement

This study does not involve any kind of human and animal trial.

Abstract

A novel coronavirus unexpectedly erupted in Wuhan, China, in December 2019, triggering human-to-human transmission. As a result, there was a massive outbreak of respiratory disease in that region and this coronavirus became a lethal pathogen within a brief amount of time, causing an epidemic and later becoming a global pandemic. The disease caused by the novel coronavirus is named as Corona Virus Disease 2019 (COVID-19). There is no realistic therapy for permanently curing COVID-19 at this stage. However, various medicines demonstrate improved outcomes against the virus, but it is also suggested that this pandemic could be avoided by a potential vaccine. There are currently several ongoing initiatives for the production of a vaccine, with some of the candidates displaying encouraging results. ChAdOx1 nCoV-19 is the most promising candidate among them. Therefore, the primary goal of this research is to analyze the potential solutions and effects of the existing vaccine candidates and to highlight that the ultimate solution will be vaccine.

Keywords: vaccine, vaccine candidates, coronavirus, challenges, COVID-19 vaccine; COVID-19 vaccine structure

Dedication

Thanking Allah, I dedicate my work to my Parents, and my wife who have sacrificed their happiness in fulfilling my dreams.

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List of Acronyms

SARS-CoV-Severe Acute Respiratory Syndrome Coronavirus

MERS-CoV-Middle East Respiratory Syndrome Coronavirus

ACE2- Angiotensin Converting Enzyme 2

HE- Hemagglutinin Esterase

ADE-Antibody Dependent Enhancement

HLA-Human Leukocyte Antigen

HCT-Human Challenge Trial

CTL-Cytotoxic T Lymphocytes

DNA- Deoxyribonucleic acid

tRNA- Transfer Ribonucleic Acid

ICTV -International Committee on Taxonomy of Viruses

PCR- Polymerase Chain Reaction

NSP- Non-Structural Proteins

EM- Electron Microscopy

ARDS- Acute Respiratory Distress Syndrome

TMPRSS2- Transmembrane protease, serine 2

aAPC- Artificial Antigen-Presenting Cells

FDA- Food Drug Administration

EUA- Emergency Use Authorization

R&D- Research and Development

HIV- Human Immunodeficiency Virus

Hib- Haemophilus Influenzae Vaccine

CHIM- Controlled Human Infection Model

EMA- European Medicines Agency,

USFDA- The U.S. Food and Drug Administration

cGMP- Current Good Manufacturing Practice

MHRA- The Medicines and Healthcare products Regulatory Agency

Chapter 1

Introduction

1.1 **Virus**

Viruses not only have a great propensity to become life-threatening but also it even causes human beings irreparable damage. (Belete, 2020a).

In the late 19th century, the groundbreaking work that relate microbes to particular plant and animal diseases, before that management of disease outbreaks especially animal disease was not practicable. Most relate, the beginning of virology occurred when the research was done on the spread of the tobacco mosaic virus by Ivanofsky and Beijerinck (1892-1898). Both researchers were able to demonstrate the propagation of the agent which is responsible for causing disease in tobacco plants. They used fluids that moved through bacteria-sparing filters to demonstration. Additionally, at the same time virtually the veterinary virology era was started when Beijerinck characterized the transmission of tobacco mosaic virus. The original tobacco mosaic virus experiments contributed to greater knowledge of "filterable agents," including viruses (Melnick, 1972).

Under the ordinary microscopy, these are not detectable, under the normal cultivation sate they do not increase, and they slip through typical filters of bacteria. Later, it was recognized early on that their ability to passage through bacterial filters was a unique characteristic of the viruses. Many viruses, for instance Berkefeld "N" and Seitz "EK" styles, smoothly pass through the pores of

normal bacterial filters. In size and shape, they differ considerably. Small virus measurements suggest that they are outside the usual microscopic vision spectrum (Loti, 2020).

The cultivation methods used to achieve bacterial growth have been found to be unsuitable for the replication of viruses. Scientists created the poliomyelitis virus in the culture of tissues in 1948. This encourage tremendous interest to the scientists and these new cultural approaches are now widely used by them; as a result, it was possible to isolate new viruses (Loti, 2020). Viruses are easily eliminated by heat and oxidizing agents; however, they have significant resistance on drying, low temperatures, glycerin and low phenol concentrations (0.5 per cent). A variety of major human and animal infections are due to filterable viruses. Some viruses only develop diseases in humans. A high degree of immunity ensures recovery from most infectious diseases; second attacks are very rare. This susceptibility to re-infection is also associated with the presence of antibodies in the serum. The modified virus can also develop these antibodies, when experimental infection or immunization is introduced to the animals. The precise mechanism and mode of action of the antibodies remain unclear, but there is a strong similarity to bacterial antibodies according to the available data.

The reason viruses propagate is close to the same as bacteria. In certain cases, such as influenza, measles, mumps, varicose veins and chicken-pox, the transmission is primarily due to contamination of droplets or ashes. In other cases, such as rabies and psittacosis, contact with infected animals or birds can be direct; whereas direct human interaction exists in lymphogranuloma venereum and warts, arthropods are associated with the dissemination of a variety of viral diseases, e.g., yellow fever, dengue, and St. Louis encephalitis mosquitoes, louping-ill ticks, and equine encephalomyelitis mites.

The data available, especially their particulate form, morphology and ability to replicate, show that there is a good connection between viruses and bacteria in many respects. This connection is recognized by most researchers and they believe that viruses are live, the bacteria-like particulate bodies, i.e., viruses are small type of bacteria. There is gradual lack of mitochondrial activity and a higher dependency on the enzymatic systems of the tissue cells as the viruses decrease in number. However, viruses have now been known to contain either Ribonucleic Acid which is recognized as RNA or Deoxyribonucleic Acid recognized as DNA. Moreover, protein and nucleic acid that tends to be the primary genetic material is mainly responsible for genetic specificity. Therefore, in the case of the tobacco mosaic virus, the behavior of the virus is founded to be closely comparable. If it is not similar to the RNA, after significant chemical and physical care, is maintained. However, in contrast, RNA is a pure form that is contagious without protein (Loti, 2020).

In 1983, the polymerase chain reaction (PCR) was invented, which had a huge effect on virology, even though it was not related to virology. No other techniques have this much impact like PCR till this date/day. Furthermore, the effect of molecular techniques on the detection and diagnosis of viruses was however founded by the molecular recognition of the hepatitis C virus without doing isolation or in-vitro culture of the virus. Few viruses for instant, papillomaviruses, noroviruses, rotaviruses, and some nidoviruses that cannot be readily grown in vitro can now be characterized and regularly identified by molecular tests. Viruses, however, were instruments for studying the fundamental biochemical processes of cells, as well as transcription of gene and translation, as time went by. Moreover, viruses have certain protective characteristics which can be used for beneficial reasons.

In a very negative sense, viruses have historically been seen-illness-inducing substance that must be either regulated or destroyed. This was clear that the filterable substances could not be grown on culture plates, and the test of time was defined by this particular feature, and all of the viruses are obligatory intracellular parasites. Although, not all obligatory intracellular parasites are viruses. By comparison, viruses have deficiency of all the metabolic abilities needed to replicate, including the creation of energy and the processes used for protein synthesis. With related ribosome, it does not possess normal cellular organelles of normal cells, for instance mitochondria, endoplasmic reticulum, chloroplasts, and Golgi.

Viruses are inactive particles outside the living cell, while the virus uses host cell processes within the cell to generate its nucleic acid and protein for producing the next cycle of viruses. The protein coding ability of viruses varies from couple of proteins to almost thousand. Although, the spectrum of complexity mainly illustrates the different influences on the metabolism of the host cell of viral pathogens, but hence, the consequence of an infection remains the very same which creates more descendants' viruses. Another characteristic of viruses is binary fission, a form of asexual reproduction where a preexisting cell separates into 2 similar daughter cells, does not replicate them. The replication mechanism for virus is basically similar to an assembly line where several small units of the virus fall one after another, so that it can form new particles of the virus that is being derived from varies parts of the host cell. At first, it enters the cell immediately after the virus binds to a host cell and the particle of the complete virus stop to function. After that, the viral genome leads the creation of novel viral macro-molecules, eventually starting the reemergence of particles of the new descendent virus.

In the nutshell, viruses only possess either RNA or DNA nucleic acid that carries the virus replication material. However, it is now apparent that certain viruses contain non genomic nucleic acid molecules. Early research characterized viruses by their small size, but viruses that are physically bigger than certain mycoplasma and rickettsia have now been described. (Melnick, 1972)

1.2 **Morphology of virus**

For characterizing viruses, early efforts involved were hindered by the lack of adequate technologies. For instance, two basic experiments were conducted for the agents of novel disease for almost 40 years which involves filtration and susceptibility to chemical agents. However, using an electron microscope, it was not until 1939 that a virus was visualized. As a rod-shaped molecule, the Tobacco mosaic virus emerged, revealing the particulate existence of viruses. The invention of negative stain electron microscopy was a significant advance in determining virus morphology in 1958. Electron-dense stains involving in this technique mainly cover those particles of the virus for creating a negative virus image with increased resolution.

1.3 **Structure of a Virion**

The virion being the complete unit of a simple virus, includes only one nucleic acid like DNA or RNA molecule in which a morphologically well define capsid is surrounded and also it is composed of subunits of viral protein that known as virus encoded polypeptides.-Moreover, the subunits of proteins are possible to be self-assembled into multimer units which is also known as

structural units and also it can contain one or more chains of polypeptides. However, possibly the detection of complexes that misses a nucleic acid is mainly refer to them as empty capsids. Moreover, the definition of the word nucleocapsid is somewhat not clear. Therefore, it is confirmed that a capsid along with its nucleic acid can be refer as nucleocapsid where on the other hand, the virion is also the structure for basic viruses such as poliovirus. The nucleocapsid mainly described to be a structure which is consist of a single strand of RNA that is complexed into a viral protein. Moreover, this protein mainly forms a helical shape for paramyxoviruses. However, by extracting a lipid envelope which is introduced from the host cell membranes can be modified by adding the viral proteins where the nucleocapsid is particularly assembled into a complete virion. (Melnick, 1972)

1.4 Evolution of the virus

Almost all initial victims had animal exposure at the onset of the SARS outbreak prior to disease progression. However, antibodies of Severe Acute Respiratory Syndrome were not only detected in the palm civets (*Pagumalarvata*) but also founded in the animal caretaker which were present in a remote market place after the SARS pathogen was identified. However, further studies were subsequently carried out to explain that SARS-CoV strains detected in consumer civets were transferred from other to them. Moreover, two teams independently identified the identification of new human-related SARS-CoV. The coronaviruses that referred as SARS-CoV-related viruses or coronaviruses like SARS in bats like horseshoe are founded to be following this incidence (genus Rhinolophus). However, these results altogether suggest that bats can be the SARS-CoV primary hosts and also that civets are simply intermediate hosts. Later, bats were founded to have multiple SARS-CoV coronaviruses (Shereen et al., 2020).

1.5 Family of Coronaviridae

The Coronaviridae family members include a large, enveloped and single stranded RNA of the virus. They are the largest RNA viruses known, with virion genomes ranging from 25 to 32 kb and 118-136 nm diameter. Not only is the shape of the virions approximately circular, but also the broad spike glycoprotein extending from 16 to 21 nm. There are two subfamilies of the family, the Coronavirinae and the Torovirinae. However, Members of the Coronavirinae subfamily are very common in mammalians and most importantly it is the only cause of enteric infections mild respiratory. However, about 60 bats (BtCoV) already have isolated from coronaviruses and unfortunately most of these viruses are founded to be belong to betacoronavirus family. Therefore, all the members of the subfamily of Coronavirinae are very common in mammals and most probably this can be the only cause of enteric infections or mild respiratory. (Payne, 2017)

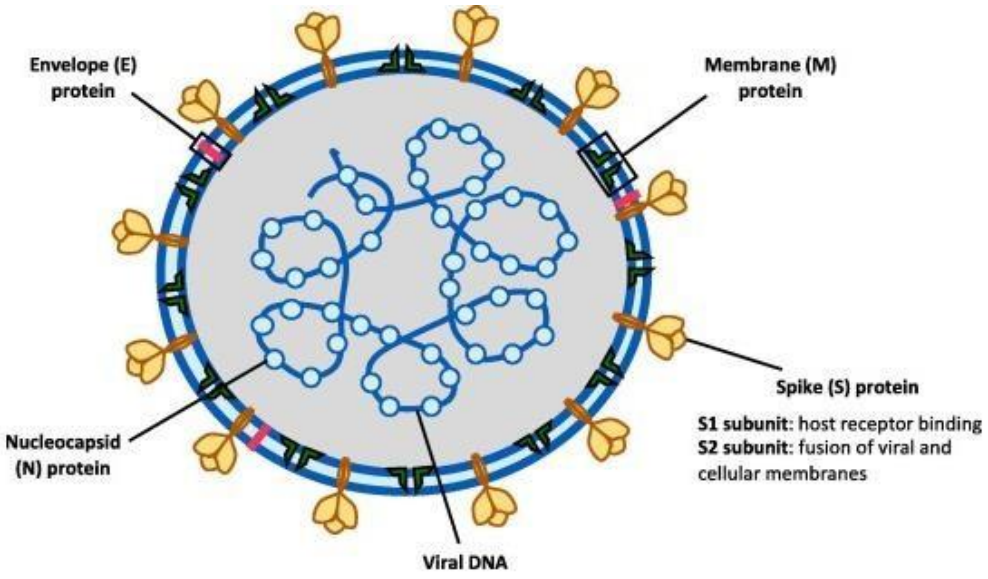
1.6 Introduction of Coronavirus

SARS-CoV-2 are the species of genus Betacoronavirus, a class of zoonotic viruses that is known as Coronavirus which is similar to another 2 previous viruses, respectively Coronavirus known as Middle East Respiratory Syndrome Coronavirus or in short MERS-CoV and also
Severe Acute Respiratory Syndrome or in short SARS-CoV (Lai & Cavanagh, 1997). All of them are bat viruses and intermediate hosts and can jump over to induce human infection (Khuroo et al., 2020). This corona virus infection has turned into the global catastrophe, which was founded in the last month of 2019 that originated from Wuhan, China. The latest virus has been labeled as Severe Acute Respiratory Syndrome-Coronavirus-2 or in short, SARS-CoV-2 and also Cononavirus Disease 2019 or in short COVID-19 (Mohammad S. Khuroo et al., 2020).

The ICTV or International Committee on Virus Taxonomy subsequently referred to this pathogen also as the SARS-CoV-2. Moreover, WHO has proclaimed this new viral disease for being Public Health Emergency of International Significance on 30th of January in 2020 and also officially labeled it as COVID-19 or Coronavirus Disease 2019 on the date of 11th of February in 2020. Chakraborty & Parvez, 2020).

1.7 Structure of corona virus

The composition of the SARS-CoV-2 is mainly a relative broad genome which is about 30 (2632) kb pairs (Belete, 2020a). It is enclosed in an icosahedral protein container (Lai & Cavanagh, 1997). It also has non-structural proteins like NSP12, NSP3, NSP13 and NSP5 which are vital for not only its life cycle but also in pathogenesis. Four structural proteins named the envelope protein, nucleocapsid protein, S-spike protein or outer spiky glycoprotein, membrane glycoprotein and nucleocapsid protein are present in the SARS-CoV-2 virus, as well as other CoVs (Lai & Cavanagh, 1997). These proteins enable the interactions between the corona virus and the host cell to establish an ideal environment for replication, modify the induction of the host gene, and neutralize the antiviral defense mechanism of the host (Lai & Cavanagh, 1997). On the surface, there are club-shaped spikes that generate the appearance of an electron microscopy (EM). The viral shell consists of a bilayer of lipids where structural proteins are incorporated into the spike (S), membrane (M) and envelope (E). Both coronaviruses use ACE2 receptors as a cell membrane entry receptor, but SARS-CoV-2's ability to adhere to these binding sites is much stronger, leading to higher infection. (Khuroo et al., 2020).



The spike protein (S) binds to the host receptor for the transmembrane ACE2. Along with the membrane (M) protein, the envelope (E) protein shapes the viral envelope and controls its shape. The hemagglutinin esterase (HE) enzyme resembles another cell entry pathway. The protein nucleocapsid (N) is eventually bound to the RNA genome of the virus to form the nucleocapsid.(Koirala et al., 2020).

Figure 1:.Structure of SARS-CoV.

1.8 SARS-CoV-2

Research teams synthesized and discovered a new β-coronavirus, which has 86.9 % similarity of the genome to an earlier reported bat SARS-CoV like genome that is marked from human SARS-CoV and MERS-CoV, following the unexpected wide-spreading of the novel coronavirus.

SARS-CoV-2 affected patients reported a number of manifestation, which include dry cough, pneumonia, , fatigue, and fever, with approximate mortality rate of 3% to 5% for people who were infected with SARS-CoV in the year of 2003 and with MERS-CoV in the year of 2012 (Lan et al., 2020).

COVID-19 (coronavirus disease) is a recently discovered coronavirus-induced, developing disease. It may lead to serious illness and death, particularly for individuals in groups at risk. A number of symptoms of differing severity are found in COVID-19. There is also an asymptomatic outbreak, and about 20-30 % of individuals who do have the virus are likely to show no symptoms. Symptoms are mild for about 40 % of individuals who have symptomatic COVID-19, without hypoxia (low blood oxygen level) or pneumonia.

40 % have mild symptoms of non-extreme pneumonia, another 15 % have serious diseases, as well as severe pneumonia, and 5 % have life-threatening conditions that are critical diseases. Moreover, there is increasing evidence that there could be longer-term impacts, such as rare neurological and psychiatric complications, in those who develop critical COVID-19 disease. These could include stroke, delirium, anxiety, depression, brain damage or inflammation, and disturbances of sleep. For more detail on frequently recorded conditions and resources required for COVID-19 patients to recover, refer to the long-term health effects guidance. A greater chance of contracting extreme or critical COVID-19 disease is correlated with certain risk factors. (Coronavirus

COVID-19 | Vaccine Knowledge, n.d.)

Higher chance of developing severe or critical COVID-19 disease can be influenced by the following factors.

- Increasing of human age
- Male human
- Complex health conditions of individual
- Clinically extremely vulnerable related to respiratory condition
- Weak immune system
- Various culture and groups, such as black, ethnic or minority group
- Job related to health and social care

(Buitrago-Garcia et al., 2020)

1.9 Symptoms of COVID-19

COVID-19 can cause a series of symptoms of varying severity. Certain patients with COVID-19 do not show any symptoms, and this is called an asymptomatic infection. In about 40 % of those who acquire COVID-19, the symptoms are moderate and without hypoxia (low blood oxygen) or pneumonia.

Main symptoms (most of the people have at least one of these symptoms):

- Rising body temperature
- Constance coughing
- loss of sense, result changes of smelling or tasting sense

Secondary symptoms:

- breathing difficulties because of short breath
- Fatigue
- decrease of appetite
- Muscle ache
- Sore throat
- Pain in the head
- Nasal congestion
- Diarrhea, nausea and vomiting

- Older and immunocompromised people may develop atypical symptoms, often in the absence of a fever.

- Delirium

- Reduced mobility

High fever, cough, sore throat, shortness of breath, weakness, rhinorrhea, and dyspnea define the COVID-19 disease. Researchers have found that these symptoms are not unique when opposed to general pneumonia. Neurological indicators such as myalgia, dizziness, anosmia and ageusia are seen in SARSCoV-2 infection patients. Some had stomach problems, which are also found in some patients, such as diarrhea. The majority of the patients on admittance had non-specific symptoms. SARS-CoV-2 infection was more proportional to mild and serious disease in patients with renal problems. (Yang et al., 2020).

1.10 Community Transmission of Severe Acute Respiratory SyndromeCoronavirus-2

Depending on recent findings, it is suggested that COVID-19 transfers among individuals by close interaction with affected individuals through nose and mouth secretions, and indirect or direct contact with contaminated objects or surface. Including saliva, secretion of respiratory or droplets.

These include mainly respiratory or saliva secretions or secretion of droplets. This are expelled either from the nose or from the mouth as an infected human sneeze, coughs or talks. Near encounters (less than 1 meter) to an infected person may cause other people to have COVID-19 as the droplets enter their mouth, nose or eyes (Cabore et al., 2020). Individuals with the virus can transmit infected droplets, known as fomites, on items and structures from their noses and throats.

However, through contacting these objects or surfaces and after that, touching their noses, eyes or mouths, others can become easily infected, if they don’t wash their hands. Any surgical operations can contain very small droplets, known as aerosols, which can stay floating for prolonged periods

of time in the air. In these aerosols, the COVID-19 virus can be found. These aerosols can theoretically be inhaled by others if individuals do not wear personal protective equipment.

Moreover, in some closed environments like restaurants, places of worship, nightclubs or places of work where people meet each other on regular basis, the outbreaks of COVID-19 have been reported recently. The socio-ecological context that affects the propagation of disease is assumed to impact these routes of dissemination by which the virus will spread. Population density, temperature, population movement, social behavior, etc. these are some of the variables that allow the virus to spread rapidly. Finally, looking at SARS-CoV-2 severity, it is indicated that older age, male gender and clinical comorbidity are associated with more serious disease. (Liu et al., 2020).

1.11 Objectives of This Review

The main objective of this analysis is to give a timely summary of attempts to create a vaccine for the current 2019 coronavirus SARS-CoV-2.

Objective 1: To understand not only the types of vaccine for SARS-CoV-2 but also vaccine platforms that are being developed.

Objective 2: To Obtain knowledge of the issues regarding the production of coronavirus vaccines.

Objective 3: Acknowledgment of the issues of accelerated development of vaccines in pandemic situations.

1.12 Significance of the study

The ongoing SARS-CoV-2 outbreak throughout the world has resulted in extreme pressure on researchers for urgent and rapid vaccine development. In this paper, the brief introduction of viruses and different vaccine candidates within different phases of development is discussed in which SARS-COV-2 is the main context. Vaccines for the pandemic disease development precepts present a unique model. There are different stages in the development and production process of an effective vaccine that require a considerable amount of time before it can be given to people. While multiple vaccines have completed the COVID-19 vaccine phase trials, there are several efforts to produce a COVID-19 vaccine in the hunt for and in the chase. Nearly 123 vaccine candidates are worldwide in current development and testing and at least 8 vaccines are currently in the phases of human clinical trials.

Chapter 2

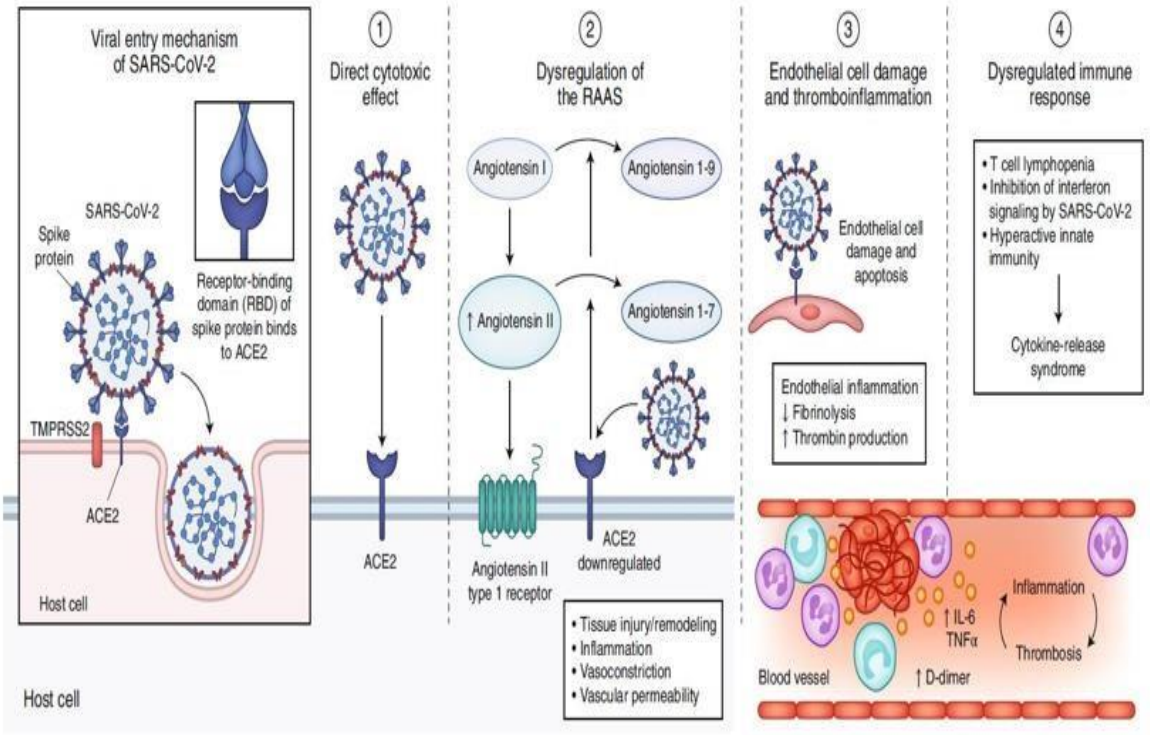
Literature review

2.1 Pathogenesis of COVID-19

Clinical and immunological development indicates that COVID-19 can be separated into 3 phases. At first, it creates flu-like diseases with a heavy viral load. Afterwards, it will turn into a crucial phase that will reduce the rapid inflammatory response of viral titers and cause lung and other organ damage. Finally, fibrosis characterizes the last stage of the disease (Polak et al., 2020). SARS-CoV-2 titers remain elevated with symptoms throughout the first week in nasopharyngeal and endotracheal aspirate specimens, followed by a steady decline starting at the end of the first week. In the small sequence, there was no disparity in viral loads between minor and extreme diseases. In those with more acute illnesses, there is a less steep and sustained decline in viral titers. It is advised to decrease the number of helper T-cells, T-cells, and memory helper T-cells during the process. The combined effect of the cytopathic symptoms caused by the virus and immune-mediated damage is demonstrated by constant high virus titers, incorrectly determined by deficient immune systems with elevated cytokine levels. Patients can succumb to illness or eventually heal during the critical phase. The choice of medicinal agents varies at various stages of illness. Viral loads and cytokine concentrations are currently not recorded in children with COVID-199 (Dhochak et al., 2020).

2.2 Mechanism

If SARS-CoV-2 targets some cells that express not only angiotensin-converting enzyme 2 but also receptors of TMPRSS2 surface, virus replication occurs successfully and release is induced in the host cell so that it can undergo pyroptosis and also it release molecular patterns which is associated with damage along with nucleic acids, ATP and also ASC oligomers (Joly et al., 2020). Moreover, endothelial cells, adjacent epithelial cells and alveolar macrophages accept these elements. They cause different pro-inflammatory cytokines and chemokines to be produced. These proteins draw the infection site of monocytes, macrophages and T cells, inducing more inflammation. After that, they set up a feedback loop of pro-inflammatory. When a defective immune response occurs, it may further turn to an aggregation of immune cells in the lungs that induces pro-inflammatory cytokines overproduction, thus destroying lungs' structure. Then the cytokines circulate to other tissues which results in damage to the several organs. (Tay et al., 2020).



Chronology of events during the infection of SARS-CoV-2. (1) Direct virus-mediated cell damage occurs after SARS-CoV-2 reaches host cells through the interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2.After that (2) RAAS dysregulation occurs as a consequence of viral entry-related downregulation of ACE2, resulting in decreased cleavage of angiotensin I and angiotensin II. (3(4) These eventually lead to endothelial cell damage and thromboinflammation, dysregulation of the immune response, and hyperinflammation occurs through interferon signaling inhibition of the virus, lymphodepletion of the T cell, (adapted from Gupta et al., 2020).

Figure 2: Chronological steps of infection of SARS-CoV-2

2.3 Vaccine

The protein structure of SARS-CoV-2 has been found, which should enable medical countermeasures to be quickly produced and tested to resolve the emerging public health crisis. Such results provide the basis for further studies to develop vaccine strategy for this new virus. Most coronavirus vaccines are targeted at the spike (S) glycoprotein protein. Vaccine production is a lengthy process and there are no appropriate vaccines accessible at the time of a pandemic outbreak. Fortunately, Moderna announced on 24th February in 2020, that the new mRNA COVID-19 vaccine, recognized as mRNA-1273, is prepared for human trials. The protection and immunogenicity clinical trials of Moderna vaccine in the management of COVID-19 is being studied (Zhai et al., 2020). SARS-CoV-2 vaccines were developed even faster than Ebola vaccines thanks to the collaborative efforts of scientists around the world and the fast-track adoption of SARS-CoV-2 vaccine production efforts by Chinese health organizations. Nonetheless, although recently no fresh incident has been identified in the past 17 years, research related to the improvement of the SARS vaccine did not achieve its distinct traction. Meanwhile, several research groups have developed many strategies for vaccinating against coronavirus diseases, including

1. Live attenuated,
2. Inactivated vaccine,
3. Protein subunits,
4. Viral vector platforms.

Moreover, it is also a skillful, troublesome and difficult task to produce the vaccine over a limited span of time, which can typically take an average of 1.5 to 3.0 years. (Badgujar et al., 2020).

In populations, a vaccine has the ability to produce herd immunity, which can minimize the occurrence of disease, block transmission and decrease the economic and social risk of illness. Higher immunization coverage is needed to successfully tackle the pandemic, both to avoid secondary waves of infections, and to manage seasonal outbursts of endemic infection. Subsequently, as with many other diseases which have greater capacity than COVID-19 to cause pandemics such as smallpox, and so on the disease may be eradicated (Khuroo et al., 2020).

2.4 Vaccine immunology

The quest for an appropriate anti-virus drug or the subsequent infection has been intensive and did not lead to any groundbreaking products. To end the pandemic, a drug that is at least 95 % effective is what we need. This and other medicines can save lives, but there is nowhere near the potential to return regularity to the chaos produced by the pandemic. Therefore, an appropriate and secure vaccine must be produced as soon as possible and made available at a reasonable price to all countries and communities threatened by the pandemic. Vaccination is capable of producing herd immunity in populations, thus reducing the transmission of viruses, blocking the spread and reducing the disease's economic and social effects. Quite high coverage of immunization is capable of fighting not only the pandemic but also to prevent secondary waves of infection and to control infection outbursts of seasonal endemic. Therefore, as has occurred for many other viruses that have had a much larger ability than COVID-19 to cause pandemics such as smallpox, poliomyelitis, etc., the outbreak can only be eradicated by an appropriate vaccine.

2.5 Importance of vaccine

Vaccines have had an outstanding positive impact on the well-being and health of the public. In present days, we desperately need vaccines to save individuals from the latest coronavirus pandemic (the source of Covid-19 disease is SARS-CoV-2), and it is a clear reminder of the significance of vaccines and the necessity of being able to improve and extend their use in a timely fashion. In fact, not only can vaccines save lives, but they can also avoid the effects on the global economy of infectious diseases, which have so far killed more than 600,000 individuals and have caused 25 million people to be unemployed in the US alone. (Black et al., 2020)

The best bet for the treatment of COVID-19 is vaccination. Some of the biotechnological platforms on which the search for a global vaccine is concentrated are mRNA, epitopes, DNA plasmid, and artificial antigen-presenting cells (aAPC). Apart from EUA vaccines, there is currently no FDA-authorized vaccines for COVID-19. There is inadequate knowledge of the basic antigens used in the manufacture of vaccines for SARS-CoV-2. The majority of candidate vaccines are intended to cause viral spike (S) protein neutralizing antibodies that inhibit its absorption through the ACE2 receptor. If a clinically successful SARS-CoV-2 vaccine is to be made available for use within 12-18 months, the dramatic change from the traditional manufacturing pathway of the vaccine would be reflected if the journey from the laboratory to the market is unhindered. This will involve a multi-pronged approach including emerging paradigms of vaccine growth, agile stages of development, ramping up current production capability, unparalleled global R&D size and speed, and fundamental improvements in regulatory processes. Any phase of the way, proper assessment of protection and effectiveness would also be needed. (Chakraborty & Parvez, 2020)

Several attempts have been made to create COVID-19 vaccines to combat the pandemic, and the S-protein of SARSCoV-2 was used for most of the emerging vaccine candidates (Dhama et al., 2020). As of January, 2021, 237 vaccine candidates are included in the worldwide SARS-CoV-2 vaccine landscape, of which 173 are in the preclinical or exploratory stage of production and 64 in the clinical development stage. Presently, few promising phase III clinical trials include, Ad5-nCoV (CanSino Biologicals), INO-4800
(Inovio, Inc.), Matrix M1-Adjuvent Novavax, and Bharat Biotech International Limited (COVAXIN) (BBV152) (WHO, 2020)

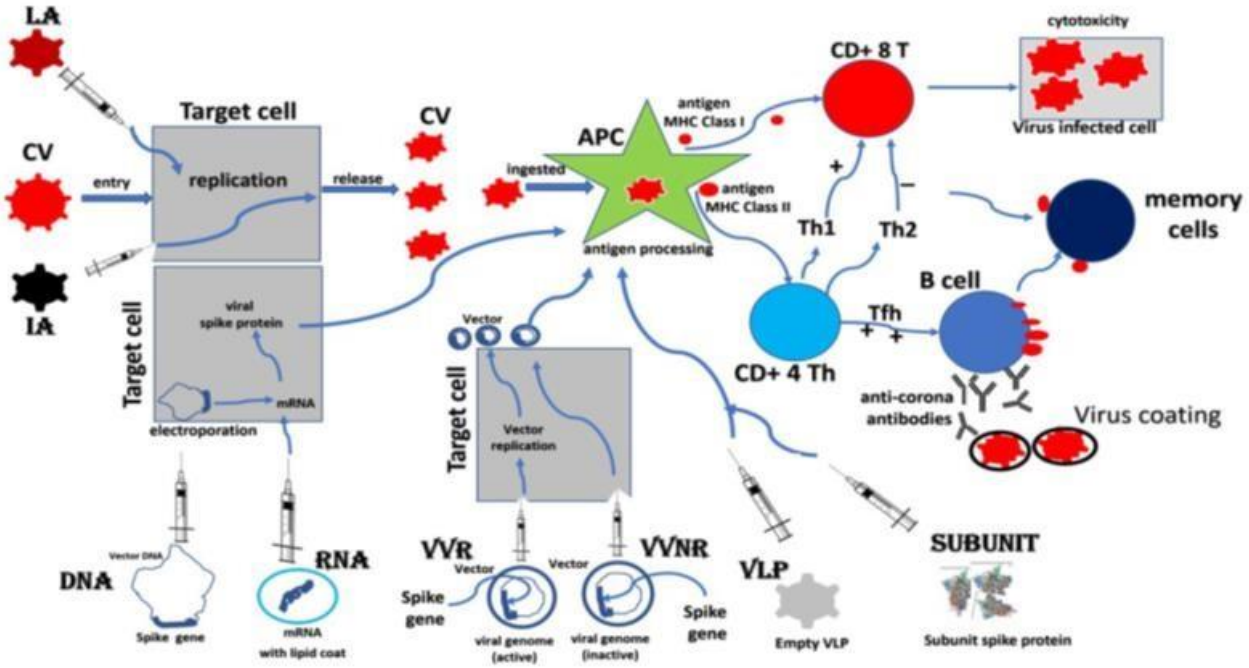
Chapter 3

Vaccine strategies

3.1 Principle

To detect and fight pathogens, a vaccine operates by preparing the immune system, whether viruses or bacteria. To do so, in order to induce an allergic response, certain pathogenic compounds must be inserted into the bloodstream. Such compounds, present in both bacteria and viruses, are referred to as antigens. Through inserting these antigens into the host body, making antibodies and recalling them for the future, the immune system can quickly learn to recognize them as hostile invaders (HCVG15-CHD-158, 2018). The immune system detects the antigens automatically when the bacteria or virus reappears and actively targets them well before the pathogen can spread and cause disease. Vaccines are preparations of weakened or killed viruses or viral subunits which induce unique protective immunity. The achievements of the eradication campaigns for smallpox and poliomyelitis and the rise of illnesses for which no appropriate vaccine is available show that vaccination is the single most effective tool for eliminating communicable diseases like human immunodeficiency virus, hepatitis, malaria, worms and tuberculosis. A vaccination is capable of creating immunity for population herds, which minimizes disease incidence, reduces illness and minimizes the disease's social and economic effects. Extremely increased amounts of immunization can effectively counteract the pandemic, reduce secondary disease outbreaks and control seasonal endemic disease outbreaks. Vaccinations help to develop immunity by mimicking an infection. However, this form of infection almost never induces vomiting, but it causes T-lymphocytes and antibodies to be produced by the immune system. Often, after receiving a

vaccine, an artificial infection may generate mild manifestation, for example fever. These negligible indications are typical and can be expected to develop as immunity builds up in the body. Vaccines help to develop immunity by imitating an infection. However, this form of infection almost never induces illness, but it stimulates the T-lymphocyte generation of the immune system and once the false infection is gone, the body is left with a supply of T-lymphocyte 'memory,' as well as B-lymphocytes that can learn how to fight this disease throughout the future. And then, after vaccines, it usually takes the infected body a few weeks to emerge T-lymphocytes and B-lymphocytes. As the vaccine did not have enough time to guarantee safety, a person afflicted with a disease may still be able to develop symptoms and become sick either before or just after vaccination. (Burns et al., 2007).



Vaccine methodology. A visual overview of the 8 system strategies for the development of COVID-19 vaccines and the process followed to induce T cell and B cell immune responses. Live-attenuated (LA) vaccine, inactivated (IA), the techniques are DNA vaccine (DNA), RNA vaccine (RNA), viral vector replicating vaccine (VVR), viral vector non-replicating (VVNR), virus-like particles (VLP) and subunit vaccine (Subunit). CV shows coronavirus, while APC shows antigen processing cells(adapted from Khuroo et al., 2020).

Figure 3:Various type of vaccine methodology.

3.2 Vaccine components

3.2.1 Adjuvant

An adjuvant is a material that adds to the vaccine producing process to enhance the immunogenicity of the vaccine. This is often a mandatory incorporation since antigen purification can contribute to the degradation of its intrinsic adjuvant properties. Currently, adjuvants are still a big issue in terms of vaccine protection, with mercury-based (thiomersal) adjuvants gradually being removed, and concerns regarding aluminum-based adjuvants (without any specific basis) are also growing. Several vaccinations hold aluminium salts, for example

1. Aluminium hydroxide,
2. Aluminium phosphate or
3. Aluminium sulphate potassium.

They act as adjuvants, enhancing the vaccine's immune response and prolonging it. Pig-derived gelatin is used in some live vaccines as a stabilizer to prevent live viruses from temperature damage. Gelatin that is broken down by water is heavily refined and hydrolyzed in vaccines, thereby distinguishing it from the usual gelatin found in foods. (Bastola et al., 2017).

3.2.2 Active ingredients

It comprises components of bacteria or viruses known as antigens. Small quantities of active ingredients are used in vaccines; just a few micrograms per vaccine (millionths of a gram). Vaccine includes whole bacteria or viruses. In both cases, bacteria or viruses are either significantly weakened (mitigated) or totally killed (inactivated) so that they will not cause illness in healthy individuals. Most vaccines only carry pieces of viruses or bacteria, usually surface proteins or sugars. These activate the immune system but are unable to induce disease. (Eagle & Gad, 2014).

3.2.3 Preservatives

These preservatives are essential for the distribution purpose of the vaccine. Moreover, it guarantees immunogenicity and overall effectiveness of the vaccine. In addition, it also increases the shelf-life of the vaccine. (Barbara E Eldred, Angela J Dean, 2006).

3.2.4 Stabilizers

Like sugar or gelatin, it helps the active ingredients in the vaccine continue to work when manufacturing, refining, and transporting the vaccine. It prevents the active ingredients of vaccines from changing because of something like a temperature difference. (Eagle & Gad, 2014).

3.3 Reason behind the lengthy of vaccine development

Between the original science breakthrough and vaccine licensing and policy decisions, 15-20 years are typically expected. Because, in traditional way national regulatory authorities, policymaking bodies and manufacturers require a significant number of clinical trials prior to licensing and recommendation; however more recently, additional post-licensing studies also be needed for vaccine use. (Black et al., 2020)

Every new vaccine must be followed a strict Research and Development (R&D) protocol carefully and completed before it is licensed for marketing. Unlike other medications, every vaccine must go through heavy and vigorous testing to ensure that it is safe before it can introduce to a country. However, before doing that a vaccine must be tested on animals to evaluate its safety and potential to prevent disease. And then, it is tested in human clinical trials in three different phases. (Vaccines and Immunization: What Is Vaccination, n.d.)

3.4 Discovery and Early Development

A variety of technical advancements are now making it possible to significantly accelerate vaccine development early phases. For example, the accessibility of the nucleotide sequences enables synthetic genes and nucleic acid vaccines to be produced in a week for laboratory research. Furthermore, the accessibility of the atomic structure enables tailored antigens to be structurally constructed in the same period of time. Moreover, it has been found that early knowledge of diseases from the global epidemiology is given advantage by high-throughput study of not only the genomes from bacteria but also both viruses and parasites which are isolated worldwide. In the meanwhile, the early advantage is also given by the discovery of both monoclonal antibodies of human and structural biology; and the discovery of defensive antigens and epitopes which follows

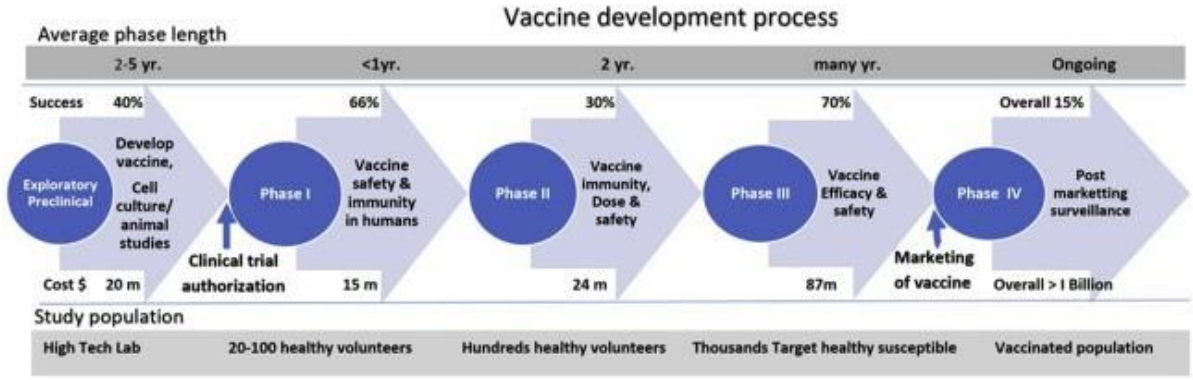
a mechanism named as reverse vaccinology. However, high-throughput research of genomes, not give early knowledge of the global epidemiology of diseases only of viruses but also give knowledge of parasites and bacteria (Rawat et al., 2020)

Prior to 2020, researchers from Oxford University have already completed a lot of work on creating a vaccine that could be modified to combat multiple diseases. That meant there were still a lot of building blocks in place, and scientists weren't starting from scratch. The vaccine has gone through all the normal processes of testing, but they have overlapped for pace as they normally occur one after another.

Guidelines relating to the therapeutic assessment of vaccines have been provided by regulatory authorities, the U.S the FDA, the European Medicines Agency and the national authorities of many countries including WHO. Usually, the vaccine development guidelines are stricter than drug development. The purpose for this is simple, because the vaccines are meant for global usage, have enormous production and marketing value and are provided to healthy populations including children, elderly people and pregnant mothers. The development of the vaccine follows a specific step-by - step process and is generally divided into these steps.

- exploratory,
- preclinical,
- clinical, and
- postmarketing steps.

Furthermore, the clinical phase is segmented into three different phases: Phases 1, 2 and 3. There are 2 regulatory permissions required before the clinical stage, namely "Clinical Trial Authorization," to allow "first-in-human" testing and "Biological License Application / Approval" for the vaccine marketing after successful clinical trials. (Khuroo et al., 2020)



Schematic drawing showing steps in vaccine development The development of vaccines follows a unique step-by - step pattern and is broadly divided into exploratory, preclinical, clinical, and post-marketing phases. The clinical stage is divided into 3 phases, Phases I, II, and III, respectively. There are 2 regulatory permissions required before the clinical stage, namely "Clinical Trial Authorization," to allow "first-in-human" testing and marketing of the vaccine following successful clinical trials.

Source: (Mohammad S. Khuroo et al., 2020)

Figure 4:Steps of Vaccine Development.

Table 1. The stages and steps of vaccine development & process.

Phases of Vaccine Development	**Aims of Vaccine Development**	**Features of Vaccine Development**
Exploratory	*Development of a vaccine.* *Vaccine development.*	• To recognize synthetic or natural antigens, extensive analysis is conducted. Attempts to develop a vaccine (Either synthetic or natural). • Time period: almost twenty-five years. • The process successful rate is about 40%. • The probable reasons of falling are depending on the pathogen's characteristics.
Preclinical	• *The vaccine is immunogenic and safe.* • *Assess the initial* dosing *for human trials.*	• Vaccine studies done on cell culture and on animals. • Challenges of studies are toxicity and antibody response. • Time: <1 year. • The process successful rate is about 33%. • Possible reasons of deficiency are underfunding, vaccine-toxicity or inadequate immune response.

Authorization of Clinical trial	• *Approval for research on human beings*	• The justification for approval and manufacturing steps and vaccine & placebo development analysis techniques. Vaccine & placebo availability and stability throughout clinical trials. • Period: between 30 days.
Phase I	• *First in-human testing.* • *Safety of the vaccine and immune response.*	• Number of volunteers with good health (20100). • In the vicinity of tertiary treatment for close observation. • Escalation study in order to avoid serious adverse effects (SAEs). • Health outcomes and production of antibody. • Time: A couple of months. • Successful rate to process is 66%. • Based on safety and immunity information, following strict go/no-go criteria.

Phase II	• *Vaccine safety & efficacy, immunity/partial* . • *Dose-response, schedule, and delivery method*	• A diverse group of people can include healthy volunteers (hundreds). • Based on the Community (university, colleges, schools, etc). • Design of the study: Studied against a placebo, adjuvant, or vaccine developed. • The vaccine is tested on various schedules and on a number of patients. • Health findings and the reaction of antibodies. In some cases, partial effectiveness results can be collected. • Time: 2 years. • Successful rate for proceeding is about 30%.
Phase III	• *Efficacy vaccination prevention*	• Subjects: Population Target (thousands). • Site: The conditions in the field are equivalent to the future application of vaccines. • Design: Randomized placebo, adjuvant or current vaccine injection vis-a-vis placebo.

		• Monitoring: Effectiveness and SAE of vaccines. • Time period: Many years. • Processing efficiency rate of 70%.
Application for Biologic License	• *Marketing vaccinations*	• Approval basis: In humans, the vaccine is safe and reliable (efficacy >95 per cent). Ability to manufacture in bulk for consumer demand. • Affordable costs for a population that is susceptible.
Phase IV	• *surveillance postmarketing*	• Reporting spontaneously (Adverse Effect Reporting System). • Monitoring: Data from end-users obtained.

Source:(Khuroo et al., 2020)

3.5 Development of Vaccine During The SARS-CoV-2 Pandemic.

Within weeks of discovering and sequencing the new coronavirus, scientists rushed into experiments on the SARS-CoV-2 vaccines. A variety of reasons, including basic scientific knowledge in the fields of genomics and structural biology and fostering a new era of vaccine manufacturing, current and newly developed vaccine technologies, research into vaccines against two other coronaviruses, SARS and MERS viruses. However, during recent epidemics, vaccine research encounters, especially Ebola in 2014-16 and Zika in 2015-16, did not go beyond phase I tests. More than 160 candidates for SARS-CoV-2 vaccines were in the pipeline by the end of July 2020, some have either completed phase 1 or 1-2 clinical trials, and a few candidates had started phase 3 trials in the summer of 2020. While shortcuts in the development and testing of vaccines could increase the pace of scientific advancement, they could also lead to efficacy, acceptability and ethical compromises. (Grady et al., 2020)

3.6 Methods

3.6.1 Live Attenuated Vaccines

Using 'wild' viruses or bacteria, live vaccines are made that have been attenuated or damaged before the vaccine is added. After immunization, weakened vaccine viruses or bacteria replicate (grow) inside the vaccinated individual. This means a relatively small dose of virus or bacteria can be administered to induce an immune response Live-attenuated vaccines usually do not cause illness in vaccine patients that have a healthy immune system. However, when a live attenuated vaccine causes' illness,' e.g., chickenpox vaccine,' that is generally milder than 'wild' disease. Live attenuated injection vaccinations typically become successful after one dose. Those given orally

generally need three doses Administration of a live attenuated vaccine may cause serious illness as a result of unregulated replication (growth) of the vaccine virus if administered to a person with a weakened reaction to the immune system, such as leukemia or HIV infection, or taking immunosuppressive medication. Live attenuated vaccines include rotavirus, measles, mumps, BCG, chickenpox and rubella. The possibility that they may induce the illness they are supposed to defend against either because they revert to virulence or because they are insufficiently attenuated for those people (e.g., those who are immunosuppressed) is one downside of living attenuated vaccinations (Baxter, 2007).

3.6.2 Inactivated Vaccines

These vaccines are produced during the vaccine making process by inactivating or destroying the pathogen. The inactivated polio vaccine is a proven example of this vaccine. This strategy includes that the virus can grow to a high titer in cell culture or other scalable medium such as hens' eggs; that the virus can be easily and completely inactivated without losing immunogenicity using an agent such as formaldehyde or B-propiolactone. In terms of viral yield

(in 10 m), the immunogenic dosage is low to intermediate from an industrialization perspective. This technique has seen excellent vaccine successes such as inactivated polio vaccine (IPV), hepatitis A (HAV) and influenza. The inactivated vaccines usually need many doses. Any inactivated vaccines can also require extra doses to maximize or 'boost' disease protection on a daily basis (HCVG15-CHD-158, 2018).

3.6.3 Toxoids vaccines

Such bacterial infections are not actually caused by a bacterium itself, but by a toxin created by a bacterium. Tetanus is an example: its effects are not caused by the Clostridium tetani bacterium, but by the neurotoxin it produces (tetanospasmin). By inactivating the antigen that triggers disease effects, immunizations can be made for this type of pathogen. As for animals or viruses used in killed or inactivated vaccines, this can be done by treating with a chemical such as formalin, or by using heat or other means. Immunizations formed by toxins that are inactivated are known as toxoids. Toxoids may be referred to as killed or inactivated vaccines, but they are also allocated their own category to indicate that they contain an inactivated toxin and not an inactivated form of bacteria. (Baxter, 2007).

3.6.4 Subunit Vaccines

In cell culture, subunits or single proteins that are prepared use recombinant DNA techniques and fermentation processes. This approach will function well where a single protein can provide immunity and where the expression mechanism demands that the viral protein be correctly folded and processed. Subunit vaccines for certain SARS coronaviruses focus on eliciting an immune reaction to the S-spike protein to avoid its binding to the host ACE2 receptor. A protein subunit vaccine requires the use of a short section of a synthetic or isolated or recombinant or highly antigenic protein base subunit antigen that gives a safer route to the formulation of the vaccine. Various protein subunit vaccines against various diseases such as influenza virus, hepatitis B, meningitis, pneumonia, etc. have been successfully developed. In the case of coronavirus vaccines, various types of proteins in full or divided form are recorded in publications concerning the binding

receptor domain or membrane protein or nucleo-capaside protein or spike protein or protein envelope. (Badgujar et al., 2020).

3.6.5 Conjugate vaccines

They're fighting off another form of bacteria. These bacteria have polysaccharides, antigens with an exterior covering of sugar-like compounds. This type of coating disguises the antigen, making it impossible for a young child's inexperienced immune system to detect and react to it. Conjugate vaccines are effective with these types of bacteria because they bind (or conjugate) the polysaccharides to antigens that the immune system reacts very well to. This interaction enables the immature immune system to react and develop an immune response to the coating. For instance, such a vaccine is the type B (Hib) Haemophilus influenzae vaccine (HCVG15-CHD158, 2018).

3.6.6 Others

Recombinant vaccines are made to produce the vaccine using bacterial or yeast cells. The virus or bacterium that has to be vaccinated against is taken from a small piece of DNA. This is injected into other cells to allow them contain significant numbers of the vaccine's active ingredient. For instance, part of the DNA from the hepatitis B virus is incorporated into the DNA of yeast cells to make the hepatitis B vaccine. One of the surface proteins of the hepatitis B virus will then be produced by these yeast cells, and this is purified and used as the active ingredient in the vaccine. This is where the latest viral vaccine will be genetically modified to incorporate genes encoding foreign virus antigens in the case of vectored or chimeric virus approaches. The chimeric vaccine

can retain strain attenuation and growth properties of the parent vaccine, but encourage immunity against foreign viruses. This is where a DNA encoding viral antigens is specifically delivered to the recipient in the case of naked DNA, plus sufficient control sequences for expression. Expression of DNA leads to an immune response against the encoded antigens (Badgujar et al., 2020).

3.7 Present SARS-CoV-2 Vaccines Platforms

Successful SARS-CoV-2 vaccines are important for handling the CoVs pandemic. At present, no vaccine has been licensed to prevent SARS-CoV-2 infection. Various manufacturing platforms of SARS-CoV-2 vaccines are available, including live attenuated viruses, viral vectors, inactivated viruses, subunit vaccines, recombinant DNA, and protein vaccines. There are some ongoing trials, but it takes months to years to manufacture SARS-CoV-2 vaccines. SARS-CoV-2 may have some promising targets at present. The COVID-19 candidate vaccines under development include S Protein or RBD subunit vaccines and replicating or non-replicating vector vaccines directly expressing the S protein or RBD. Several studies have shown that viral S protein subunit vaccines have demonstrated higher neutralizing antibody titers and protection than live-attenuated SARS-CoV, complete and DNA-based S protein vaccines. Collectively, the S protein is the preferred target site for the manufacture of SARS vaccines, and the production of SARS-CoV-2 vaccines can potentially benefit from the same strategy. (Belete, 2020a)

Table 2. *Current Vaccine Candidates.*

Type of Vaccine/Platform	**Developer/Researcher / Candidate vaccines**	**Clinical Trial Stage**
Recombinant Viral vector Unrelated virus engineered to encode the target gene of the pathogen. Viral vectors can be replicating or non-replicating	1. CanSino Biologics/ Beijing Institute of Biotechnology (Ad5-nCoV) 2. University of Oxford (AZD 1222 (formerly ChAdOx1) 3. Globe Biotech Limited, Bangladesh (**Ad5-nCoV)**	Phase III Authorized Pre clinical
Inactivated Pathogen virus inactivated by chemicals or radiation	1. Beijing Institute of Biological Products/ Sinopharm (BBIBP-CorV) 2. Bharat Biotech/ Indian Council of Medical Research/ (COVAXIN) (BBV152)] 3. Sinovac/ Instituto Butantan/ Bio Farma (PiCoVacc)	Phase III Phase III Phase III

Live attenuated Live virus with a mutated genome(s), which induces immune response but not disease.	No clinical studies	
Protein sub-unit Laboratory-produced target antigen protein components; some vaccines may use nanoparticle technology.	1. Novavax (NVX-CoV2373)	Phase III
Virus like particle Self-assembling virus modular proteins that are non-infectious	No clinical studies	
mRNA	1. BioNTech/ Pfizer/ (BNT162)	Authorized

mRNA encoding target antigen	2. Moderna/ NIAID/ (mRNA 1273)	Authorized
DNA DNA that encodes the target antigen	No clinical studies	

3.8 Role of Bioinformatics in Vaccine Designing

Among the others, the most successful infectious disease strategies of public health are Vaccines, however time to produce a new vaccine is typically takes long time, with an average production time of 10.71 years and the chance of efficacy is limited and it has only 6 % probability of market penetration. The time taken and the expense of producing new vaccines through the protection, immunogenicity and clinical efficacy processes are also unaffordable. CHIM experiments, well-designed and carefully performed, will offer insights of host-pathogen interactions, host factors identify which led to infection, identify immune correlates of disease / infection defense, and accelerate the production and testing of infectious disease vaccines and diagnostics of infectious disease. In CHIM trials, a limited number of participants may provide information on vaccine effectiveness, defense against particular pathogen strains and resistance. (Sekhar & Kang, 2020)

3.9 Clinical Trials

Each new vaccine needs to be completely safe. According to the 'precautionary principle,' the risk of side effects which bring a halt to production or require the vaccine to be removed. The cost of developing a single candidate vaccine rises by around 12 % each year and is now close to about $1 billion. The production of a new vaccine currently requires an average of 15 years. Apparently, after a single injection, vaccines will provide long-lived safety and are easy to manufacture on a large scale. Any experimental vaccine follows a stringent R&D process that must be closely observed and completed before it is approved for marketing, regulatory agencies, including the European Medicines Agency (EMA), WHO, the U.S. Food and Drug Administration (USFDA) and also Guidelines relating to vaccine clinical evaluation have been published by national agencies in many countries. The vaccine production requirements are considered to be more stringent than of those which are expected for the development of drugs. The reason is obvious, the vaccines are for worldwide use and have massive growth and marketing scope. A specific step-by-step process that is usually divided into exploratory, therapeutic, preclinical and post-marketing stages is followed by vaccine development. Three stages exist in the therapeutic phase: Phases I, II and III.

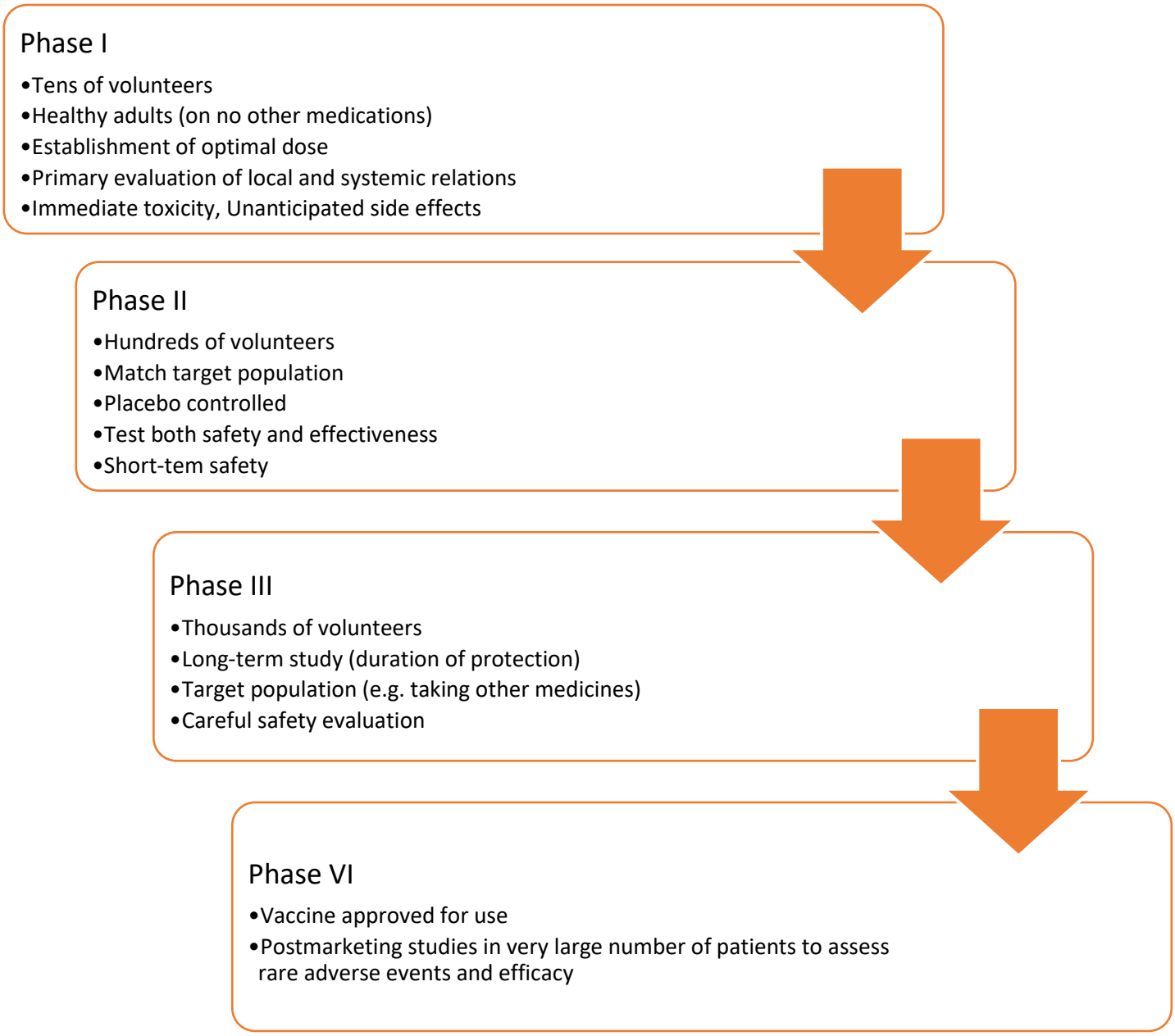


Figure 5. *Procedure of clinical testing of a potential vaccine.*

Following successful clinical trials, there are two regulatory approvals required before the clinical stage, including 'Clinical Trial Permission' to allow 'first-in-human' testing and 'BiologicLicense Application/Approval' for vaccine promotion. (Olszewska et al., 2006).

3.10 Advantages of Vaccine over other Medications

For the prevention or reduction of infectious diseases, vaccines are especially relevant. It is estimated by the World Health Organization that the measles vaccine has prevented over 20 million deaths since 2000. In the US and across the globe, vaccines have a huge effect on disease and virus control. Immunizations have converted deadly, debilitating diseases into diseases that are completely avoidable and life-threatening. It makes anyone less likely to have the illness that is being vaccinated against as more persons get vaccines. This disease prevention is considered herd immunity which protects the whole population (Nandi & Shet, 2020). The efficacy of the vaccine relates to the immediate safety offered to people under reasonable circumstances and primarily focuses on minimizing apparent effects clinically (like hospitalization, meningitis death). The primary evaluation may focus on one specific clinical manifestation where an infectious agent may induce a number of various clinical manifestations, while the secondary analysis may consider other clinical manifestations as sources of evidence. Immunizations shield us from serious illnesses and therefore discourage the transmission of those illnesses to others. Over the years, immunizations have stopped epidemics of once widespread respiratory disorders such as measles, mumps and whooping cough from arising. And because of immunizations, we've had the near eradication of others, such as polio and smallpox. As demand on public health budgets has risen over the past two decades, more innovative (and costly) vaccines have become affordable, and health economic assessment has become a significant aspect of programmed preparation for immunization. Finally, vaccines are safe and healthy. To ensure that they are effective, all vaccines are subject to long and rigorous review by experts, doctors and the federal government. (Doherty et al., 2016).

Chapter 4

Current Situation

4.1 Global Condition

As of December 2019, a number of unidentified cases of pneumonia have been reported in Wuhan city of China. Decisive steps have been taken by the Chinese government and scientists to control the disease and conduct etiological studies. This new virus was tentatively identified by WHO on 12th January 2020 as the novel coronavirus-19 (nCoV-19). After that, on 30th January of 2020, WHO declared the nCoronavirus-19 outbreak as a global public health emergency. Later, on the 23th February of 2020, there were about 77,041 definite cases of SARS-CoV-2 infection in China. Furthermore, the infection number exceeded the number of the 2002 epidemic of China's SARS. (Sun et al., 2020). In terms of speed and effects, the spread of virus and its disease was unparalleled, leading to widespread socio-economic disruption. With 3,018,681 cases and 207,973 deaths reported by 29 April 2020 in the 100th WHO situation report, it has so far outspread to all areas of the globe. (Cabore et al., 2020).

4.2 Protective Measures

4.2.1 Limiting Mass Gathering

The public health care system's vital task is to avoid spreading of SARS-CoV-2 by reducing mass gathering. COVID-19 disease is transmitted from individual to individual by mostly direct interaction and the potential transmission of this infectious disease is during mass meeting which is a significant public health concern. On the basis of previous experience of SARS & MERS infections, The WHO strongly recommended such preventive measure to limit the overall danger of spreading of COVID-19, such as, avoiding close interaction with acute respiratory disease patients, frequently washing hands by soap and water or hand sanitizer, especially after direct interaction with patients or their surroundings. Governments of various countries have resisted all kinds of religious, scientific, sporting, social, cultural, and political public assembly occurrence in various part of the globe. Many global events have also been postponed, for instant Umrah, Hajj and the Olympic Games, to prevent mass gatherings. The media and information technology provide important social support in the prevention and management of COVID-19 outbreaks. The main protective strategy for COVID-19 may therefore be the limitation of mass mixture (Sahin, 2020).

4.2.2 Global Ban on Wildlife Trade

A ban recently placed on wildlife market by China where animals are kept alive while on sale. 60% of new exchangeable pathogens arise from animals and 70% are from wild animals. Public trade of wildlife can also increase the risk of emerging novel viruses. Scientists have requested various countries to prohibit wildlife markets and exchange permanently. These interventions will help protect human lives from potential pandemics such as COVID-19. It is therefore essential to ban wildlife markets and trade globally, taking into account national security, biosecurity, and public health. (Chakraborty & Maity, 2020)

4.2.3 Personal Safety

Vaccine production is time-consuming. Many studies show that SARS-CoV-2 can spread faster than other CoV viruses. It will remain in the air for up to 3 hours, 72 hours on plastic, 48 hours on stainless steel and 4 hours on copper, much like other coronaviruses. However, while an infected person does not display symptoms, SARS-CoV-2 is the strongest multiplier in the body and can be passed on to others. The WHO and other organizations have provided some specific strategies for preventing COVID-19, including regular and careful hand washing, particularly after direct interaction with infected individuals or surroundings, avoiding touching the eyes, mouth, nose and face. When coughing and sneezing, covering the mouth and nose, taking social distance strictly by keeping a minimum distance of 6 feet from any individuals and maintaining self-isolation if ill. As proposed by manufacturers, novel coronaviruses could be vulnerable to sterilizers with proven efficacy against enveloped viruses, which include bleach (sodium hypochlorite), 70% ethanol, 0.5% hydrogen peroxide and phenolic compounds. (Ghaebi et al., 2020).

4.3 Need of a Vaccine

There will also be a risk of new disease outbreaks occurring without the SARS-CoV-2 vaccine. The coronavirus that generates COVID-19. Herd immunity can be achieved either by infecting multiple individuals or by vaccinating them. It is no wonder that many politicians and scientists see a COVID-19 vaccine as the only successful way back to health. Tracking COVID-19 spread by strict surveillance, testing, touch tracing and, where possible, quarantine or other lockdown constraints must be followed accordingly before a vaccine is widely available. The SARS-CoV-2 outbreak poses unprecedented challenges to economies and societies. The only long-term solutions that will allow populations with economies to return to normal life without needless loss of life are safe and reliable vaccines that provide people with immunity and proper care for those infected who develop COVID 19 symptoms. Although the R&D initiative has been fruitful to date, before a vaccine is available, there are still many challenges to be overcome, and treatments are widely available. International collaboration is crucial to driving change and must concentrate on the planning of manufacturing and logistics capacity, as well as on the conditions for making these innovations available and affordable to people around the world (Organisation for Economic Co-operation and Development, 2020).

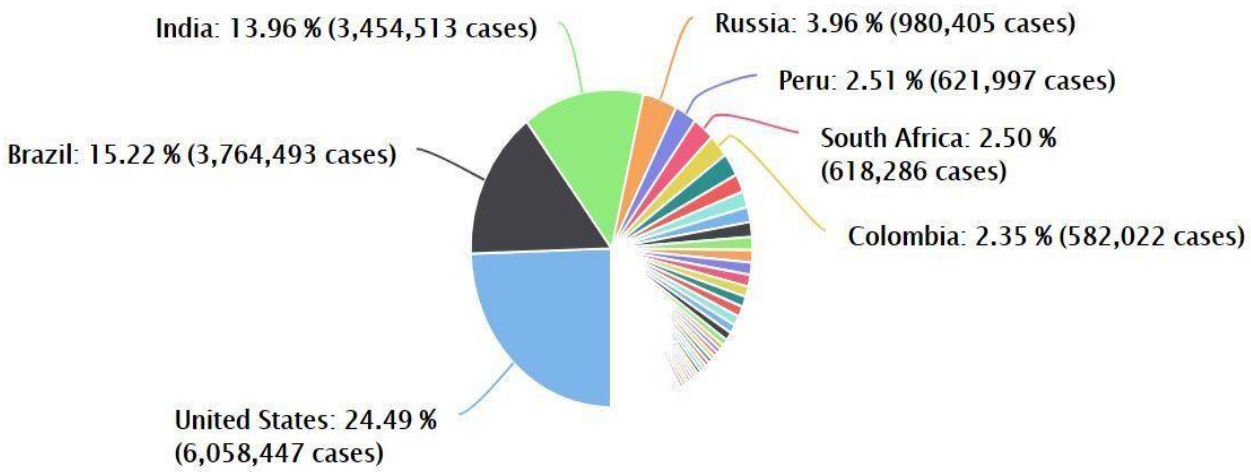


Figure 6:Current distribution cases (copied from Worldometer, 2020)

Chapter 5

Overall Situation

Most vaccine production operate for covid-19 is in the North America where potential active candidates (46%) compare with (18%) in china, (18%) in other Asian countries and Australia, and 18% in Europe. There may be variations in COVID-19 epidemiology in different geographical locations, so in order to effectively monitor the pandemic, large-scale involvement and participation of the other countries is needed, in researching and development to produce an effective COVID-19 vaccine. As China was the first to map the genome sequence of the novel coronavirus immediately after the SARS-CoV-2 epidemic, China may have a head start on developing a covid-19 vaccine. China has initiated phase 2 clinical trials with 3 vaccine candidates for a COVID-19 vaccine, with volunteers from Wuhan area. China's CanSino Bio and its collaborators were the first of COVID-19 vaccine developers to join phase II tests, only 3 weeks after the Phase I clinical study (Nagarajan et al., 2020). However, 172 nations have already been involved in negotiations so that they can potentially participate in COVAX which is a global effort that mainly aimed at partnering with vaccine manufacturers so that it can provide countries worldwide with equal access to not only safe but also reliable vaccines once they are both licensed and accepted. Moreover, COVAX not only currently boasts the world's largest but also the most extensive portfolio of COVID-19 vaccines that includes nine candidate vaccines. Furthermore, another nine are not only under investigation but also ongoing negotiations with other major producers (Dr Seth Berkley, 2020).

5.1 COVID-19 Vaccine of Pfizer BioNTech

Vaccine of Pfizer BioNTech is given in a two-dose sequence, 2nd dose is given 3 weeks apart from the 1st dose. According to safety data, where total of 37,586 participants were participated in an ongoing U.S randomized placebo-controlled multinational studies for EUA, and most of the participants were from USA. Among those participants, 18,801 of whom were given vaccine and 18,785 whom were given saline placebo. Additionally, these participants were monitored for 2 months after the administration of the second dose. 7 days after the administering of the second dose, there is no proof of having SARS-CoV -2 infection. From these clinical trials, the vaccine was 95 % effective in the prevention of COVID-19 disease. Among 170 cases of COVID-19, one was marked as serious in the controlled group and three in the randomized placebo group. There is no data available at this point to establish how much longer the vaccine can offer safety, neither is there any proof that it can stop person-to-person transmission of SARS-CoV-2 (FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine | FDA, n.d.). Data has not yet been obtainable to provide information about the timeframe of protection provided by the vaccine. (*Pfizer-BioNTech COVID-19 Vaccine Frequently Asked Questions | FDA*, n.d.)

Clinical studies have tested the safety and effectiveness of the BNT162b2 vaccine in more than 44,000 persons in 6 countries: the USA, Brazil, South Africa, Germany, and Turkey. The trial indicated that 95 % of COVID-19 cases could be prevented by the vaccine. This implies that if anyone is exposed to coronavirus in a population of 20 people who are vaccinated, 19 people will be protected from having COVID-19 when they're all exposed to coronavirus. The trial also found that the vaccine helps people of all genders, races and ethnicities with equal protection.

The BNT162b2 vaccine is a two-dose treatment that is delivered to the upper arm as an injection. The second dose should be delivered within 3-12 weeks of the first dose. (Buitrago-Garcia et al., 2020). Observed serious adverse effect was uncommon (<1.0%), although slightly higher numerical rates in the controlled group were observed compared to placebo study group, for specific kind of adverse effect. (Pfizer-BioNTech COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.). By short follow-up studies and using a large number of participants (43,448 participants; 21,720 vaccinated; 21,728 given placebo), FDA evaluated additional safe data of the vaccine. (Pfizer-BioNTech COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.)

For geographical diversity this vaccine was tested on various people:

Table 3*. Geographical diversity of a vaccine.*

Name	Percentage
Black or African American	9.1%
Hispanic/Latino	28.0%
Asian	4.3%
Native American Indian/Alaska	0.5%

However, the challenge of a Pfizer vaccine is very considerable worldwide. One study estimated that only 25 to 30 countries have ultra-cold facilities. (*The COVID Cold Chain: How a Vaccine Will Get to You - Scientific American*, n.d.)

5.2 Moderna

Extremely promising outcomes from the phase III COVID-19 vaccine trials have now been announced by two drugs producers.in 2021, on 18 November, Pfizer and its associate company BioNTech announced that their vaccine, based on complete trial data, was 95 % successful in stopping the disease. Two days earlier, based on interim results, Moderna declared that its vaccine was 94.5 % effective (*The COVID Cold Chain: How a Vaccine Will Get to You - Scientific American*, n.d.)

The EUA help data provides an overview of 28,207 participants were participated in an ongoing U.S randomized placebo-controlled multinational studies for EUA, where most of the participants had no history of SARS-CoV-2 infection before to the 1st dose of the vaccine. Among those participants, 14,134 of whom were given vaccine and 14,073 whom were given saline placebo. With 11 cases of COVID-19 in the controlled group and 185 cases in the randomize placebo group, the vaccine was 94.1 % efficient in preventing COVID-19 disease.
(Moderna COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.)

COVID-19 vaccine of Moderna is given in a two-dose sequence, second dose is given four weeks apart from the first dose. According to safety data of 37,586 participants, where participants were participated in an ongoing blinded, U.S randomized placebo-controlled studies for EUA. Among those participants, 15,185 of whom were given vaccine and 15,166 whom were given saline placebo. Additionally, these participants were monitored for 2 months after the administration of the second dose. (Moderna COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.) For geographical diversity this vaccine was tested on various group of people.

Table 4. *Geographical diversity of Moderna vaccine.*

Name	**Percentage**
Black or African American	10.2%
Hispanic/Latino	20.5%
Asian	4.6%
Native American Indian/Alaska	0.8%
Native Hawaiian or other Pacific Islander	0.2%
Identified their race as other	2.1%
Multiracial	2.1%

(Moderna COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.)

Both of placebo 1.0% (153) and controlled group 1.0% (147) participants who received Moderna COVID-19 vaccine were confirmed to have significant adverse events such as pain at the injection site, fatigue, headache, muscle ach, chills, joint pain, nausea and vomiting, swollen lymph nodes in the same injection arm, and fever were the most commonly reported side effect. Generally, the side effect began within 2 days of vaccine administration and were gone after three or two days later (Moderna COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.) No other important patterns or inequalities by age, ethnicity, gender, or medical comorbidities that may suggest a causal relation to the Moderna COVID-19 vaccine have been observed for specific forms of serious adverse effects. (Moderna COVID-19 Vaccine Frequently Asked Questions | FDA, n.d.)

5.3 Oxford and AstraZeneca ChAdOx1 nCoV-19

In 2020, on 30 December, the vaccine was authorized by MHRA for use and the 1st doses were administered only five days later. (*Covid: What Is the Oxford-AstraZeneca Vaccine? - BBC News*, n.d.)

5.4 How much effective the Oxford corona vaccine is?

The Oxford-AstraZenca vaccine has been proven to be effective and can cause an immune response in persons of all ages, including 55-year-old people, according to the BBC news. Different dosing regimens were prescribed to the patients in the study - some received 2 full doses and some half a dose, followed by a full dose. Two maximum doses, which were found to be 62 % effective, were approved by the MHRA. (*Covid: What Is the Oxford-AstraZeneca Vaccine? - BBC News*, n.d.)

In this interim review of current clinical trials, ChAdOx1 nCoV-19 has an appropriate safety profile and has been considered successful against symptomatic COVID-19. (Voysey et al., 2020). Preliminary results suggest that the vaccine is successful at 70.4 %. This vaccine 70.4 % effective, which is more powerful than the average flu vaccine, so it extremely reliable. (*FAQs about COVID-19 Vaccines | Vaccine Knowledge*, n.d.)

- Researchers have demonstrated 70.4 % average vaccine effectiveness from a combined two-dose regimen study
- No hospitalizations or serious diseases were found in the vaccinated groups within three weeks of the first injection.

- Efficacy outcomes are based on data obtained from 11,636 participants from across UK and Brazil.
- The findings of the first phase 3 analysis of a corona virus vaccine were published in peer-review literature.

The ChAdOx1 nCoV-19 vaccine has been studied on more than 23,000 persons from the United Kingdom, Brazil and South Africa by the Oxford University. AstraZeneca is currently undertaking a further experiment in the USA, Peru, Chile, Columbia and Argentina, involving 40,000 persons. Meanwhile, findings from the UK and Brazil reports have shown that 70.4 % of COVID-19 cases can be avoided by the vaccine. It was assessed with 2 separate patient groups who administered 2 non-identical dosing regimens. In addition, this vaccine has also been found to cause similar immune responses in older adults compared to young, healthy people, although there is also little evidence on the effectiveness of this population. The vaccine ChAdOx1 nCoV19 is given as a 2-doses course, and is administered to the upper arm as an injection.

The newly approved vaccines for COVID-19 have been closely examined by the MHRA in the United Kingdom. The regulatory team also performed a detailed review of the safety data reported from the trials, including several months of follow-up evidence from 23,000 individuals for the Oxford-AstraZeneca vaccine and 44,000 individuals for the Pfizer-BioNTech vaccine. This suggests that all the details from the clinical studies of these vaccines have been checked by the MHRA, which involves reviewing all the adverse effects and medical problems encountered by participants in the trials.

Since vaccines function by causing a response from your immune system, after getting the vaccine, one may experience side effects that feel close to having a true infection. Since consuming certain

vaccinations, things such as developing a fever, or feeling ache, or getting a headache (usually identified as 'flu-like' indication) are normal and it's the same with the authorized COVID-19 vaccines. Getting these signs indicate that the immune system is functioning as it should be. This signs typically stay quite a small period than a true infection and most of them are gone with 1-2 days.

5.5 The most promising vaccines

The number of cases, casualties and countries impacted by the COVID-19 epidemic is rising exponentially. There is an urgent need to identify safe and efficient ways to detect, manage, reduce and fight the disease as the occurrence of COVID-19 hits a new level every day (Awasthi et al., 2020). At present, no therapeutic agent, monoclonal antibodies, or vaccine specific to the corona virus has been approved other than (EUA). Therefore it is an urgent need of effective COVID-19 disease drugs and vaccines to limit community transmission (Belete, 2020a).Thus, drug manufacturers are attempting to develop an appropriate COVID-19 vaccine. The SARSCoV-2 vaccine is currently being produced by several countries and scientific organizations. Nevertheless, vaccine production could not be carried out immediately. Until entering clinical trials, it will undergo safety and effectiveness assessment following vaccine formulation and planning.

In general, three stages of clinical studies will assess the safety, efficacy and immunogenicity of the vaccine. Phase I experiments were performed to research the vaccine's safety and immunogenicity, and phase II and phase III research were eventually conducted for both efficacy and safety. The production of a new vaccine typically takes ten to twenty years and less than 10% effectiveness levels excepted for a vaccine that completes clinical experiments. At present, there

are also no effective vaccines to eliminate COVID-19. However, most candidates have progressed to the clinical trial and few have earned emergency authorization for use.

For example, in China, CanSino Biologicals began a phase 3 clinical trial for (NCT04341389) Ad5-nCoV in phase 1&2 clinical trials that showed safe, tolerable and immunogenic. Moderna Declares mRNA-1273 Vaccine Positive Phase 1 Interim Results. The vaccine produced virus-neutralizing antibodies in an animal model at the levels seen in convalescent serums and showed full protection in the lung against viral replication. The product vaccine for mRNA-1273 also revealed that it was stable and well accepted.

The University of Oxford has invented a mouse vaccine based on the immunogenic Chimpanzee Adenovirus Vector (ChAdOx1). In April 2020, the vaccine candidate initiated the clinical phase I/II (NCT04324606) trial in order to explore its efficacy, tolerability and immunogenicity in 510 individuals. (Belete, 2020b)

Chapter 6

Results and discussion

6.1 Results

Below are the typical side effects associated with the vaccines currently approved. Generally, these effects last 1-2 days after the vaccination.

Table 5. *Side effects of authorized vaccine candidates.*

AstraZeneca-Oxford (ChAdOx1 nCoV-19)	**Pfizer-BioNTech (BNT162b2)**	**Moderna (mRNA-1273)**
Arm Pain (67%)	Arm Pain (92-83%)	Arm Pain (91.6%)
Chills (51%)	Chills (33-58%)	Chills (43.4%)
Fever (18%)	Fever (17%)	Fever (%)
Joints pains (31%)	Joints pains (17%)	Joints pains (44.8%)
Muscle aches (60%)	Muscle aches (25-58%)	Muscle aches (59.6%)
Fatigue (70%)	Fatigue (42-75%)	Fatigue (68.5%)
Headache (68%)	Headache (50-67%)	Headache (63%)

(Buitrago-Garcia et al., 2020)

6.2 Is the Oxford vaccine as good as the Pfizer?

Studies have found that Pfizer vaccine was 95 % effective, although there were variations in terms the tests were performed, so it is impossible to compare the two findings explicitly. And it's important to note that a better outcome than the best flu jab, which is around 50% successful, is also the lower 62 % figure. What is more, because of Covid-19, no one who administered the Oxford vaccine was hospitalized or became critically ill. (Covid: What Is the Oxford- AstraZeneca Vaccine? - BBC News, n.d.)

An emergency use permit represents as the name indicates: a medicinal substance is granted special authorization by the FDA to be used in an emergency, but it is not completely approved. To be completely approved by the FDA, Pfizer will have to file a new application for the vaccine. (FDA Issues Emergency Use Authorization for Pfizer/BioNTech Covid-19 Vaccine - CNN, n.d.)

Overall, according to the document, "there are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals,"(FDA Issues Emergency Use Authorization for Pfizer/BioNTech Covid-19 Vaccine - CNN, n.d.)

Table 6. *Summary of authorized vaccine candidates.*

COVID-19 Vaccines			
	Moderna(NIAID)	**Oxford Uni-AstraZenca**	**Pfizer BioNTech**
Trails (safety effectiveness) and	15,419 participants	23,000 people	44,000 people
Suitable for	18 years old and older.	Adults of all ages shows immune responses	Strong immune responses in all tested groups
Dose needed	Two doses (0.5 mL) 1 month apart	Two doses 4-12 weeks apart	Two doses 3-12 weeks apart
Common side effects	chills; fatigue; muscle and body aches; headache;	Arm pain, Headache, Muscle aches, Chills, Fatigue	

Table 7. *Various differences between vaccine candidates.*

Company	**Type**	**Doses of vaccine**	**How Effective***	**Cost dose**	**Storage**
Oxford Uni-AstraZenca	Viral vector (genetically modified virus)	2	62-90%	£3 ($4)	Regular fridge temperature
Moderna	RNA (part of virus genetic code)	2	95%	£25 ($33)	-20C° up to 6 months
Pfizer-BioNTech	RNA	2	95%	£15 ($20)	-70 C°
Gamaleya (Sputnik V)	Viral Vector	2	92%	£7.50 ($10)	Regular fridge temperature (in dry from)

*preliminary phase three results, not yet peer-reviewed

Source: (*Covid: What Do We Know about China's Coronavirus Vaccines? - BBC News*, n.d.)

In the UK, two vaccines, following government approval, are currently in use. They are vaccine BNT162b2, developed by Pfizer and BioNTech, and the vaccine ChAdOx1 nCoV-19 (AZD1222), and developed by Oxford University and AstraZeneca. Both of these vaccines have been approved for emergency use by the MHRA, as well as a vaccine produced by Moderna, which is expected to be available from spring 2021(Buitrago-Garcia et al., 2020)

Chapter 7

Discussion

Virus is a small particle which is not visible to the naked eyes and it cannot be filtered with bacteria filter. Electron microscopy is needed to observe these viruses. These are cannot be cultivated in petridis in the laboratories, however it can be cultivated in cells or tissues. Viruses are obligatory parasite and it's behaved like non-living particle outside of the host cells. Virus composition is different from bacteria and normal cells. It lacks all the major organelles needed for producing food or replication. It only carries genetic material DNA or RNA, which responsible for replication. Virus replication occur by asexual process in the host cell, where it uses host resource to make copy of viral part and assemble parts to from new viruses. This replication process initiates when virus attach to the receptor on the host surface and insert genetic material give direction to produce new viruses. When viruses are produced, it destroys host cell and come out and infect other host cells. Virus infection can trigger the immune response of the body and it can produce antibody against the specific antigen of that viral protein.

Viruses are responsible for causing disease in human. Previously, these viruses were not visible to human and it is responsible for few pandemics. But at that time human were helpless. However, because of advancement of science and technologies, scientist can easily isolate and identify viruses. As a result, precise treatment, precaution and action can be taken,

Even with advance technologies human cannot remove from the face of the earth, because it has the ability to mutate. On the other hand, human technologies depend on this virus, for instance T2 virus is used to kill bacterial. Researchers have engineered virus to induce immunization so that virus attack can be prevented.

Nevertheless, scientist is discovering novel viruses on the regular basis and they are also trying to discover ways to fight it. Few years back, researchers have discovered a novel virus of the family Coronaviridae. It causes serious damage to the respiratory system, as a result it named SARS-CoV. However, in December 2019, SARS-CoV-2 a novel coronavirus is identified, which is similar to SARC-CoV but believed to be more dangerous. WHO declared it as international emergency on 30 January, 2020 and on 11 February, disease caused by SARS-CoV-2 is termed as COVID-19.

COVID-19 is an illness caused by the severe acute respiratory syndrome coronavirus 2(SARSCoV-2), a new form of coronavirus. Even if immunity were obtained with the help of a vaccine, 60-70% of the population will have to be immune to achieve herd immunity to SARS-CoV-2. An appropriate and healthy vaccination is needed to avoid COVID-19, and the majority of the population should be successfully vaccinated. However, in order to have global utility, the vaccine should also be quickly mass-produced inexpensively and should be easily transported and shipping ensures minimal cold chain requirements.

In order to monitor the pandemic of CoVs, successful SARS-CoV-2 vaccines are important. Vaccines limit the severity of influenza, virus replication and transmission from person to person. No vaccine has officially been approved for the prevention of SARS-CoV-2 infection other than 3(EUA) vaccines.

Several types of vaccines are currently in development stage by at least 140 internationally; in various phases including more than 15 promising candidates among them 9 candidates are already in stage 3 clinical trial for a while. Apart from this Bangladesh's globe pharmaceutical's vaccine is also promising and it is also beloved that it would be most appropriated vaccine because of regional advantage. It would be less costly and it would be easy to get.

A majority of vaccination experiments, except pediatrics, elderly and pregnant mothers, have been focused on individuals between the ages of 18-65 years. In view of the disproportionate death rate of people over the age of 60, vaccination and health-related persons in epidemic scenarios need to be considered for aged and infected and serious condition patients. The studies, however, usually did not screen for asymptomatic infection, because it is not known how many persons were genuinely resistant to infection.

A more rapid speed in the production of vaccines has never been seen in the world. The pandemic condition has prompted the traditional regulatory evaluation methods to be reconsidered; however, new advanced research and technology have made it possible to rapidly manufacture vaccines. Such us, both the Moderna and Pfizer vaccine use a new approach to active the body's immune defenses, which is messenger RNA, or mRNA. The studies, however, usually did not screen for asymptomatic infection, because it is not known how many persons were genuinely resistant to infection.

There will be major questions about the efficacy of COVID-19 vaccines as new vaccine platforms (mRNA) have never been approved before. So, we have no data is it totally safe or it might affect human in the long run, after 10 to 15 years. The past of the latest dengue vaccine in the Philippines should also encourage a degree of caution with respect to the safety of the injection during public use, even if it seems to be reliable in the Phase 1, 2 and 3 trials.

The Philippines' experience with a novel dengue vaccine should also inspire a degree of vigilance with regard to the efficacy of vaccines during population use, even though they seem healthy in step 1, 2 and 3 trials. There are numerous obstacles ahead such as, cold chain storage, genetic issue, limited time etc.

Despite efforts in fast tracking vaccine development, it would take times to reach general population and estimated time to be early 2021 to mid-2021; however, patients and healthcare persons will be prioritized. As of today, only 3 vaccines (Moderna, Pfizer and Oxford, AstraZeneca) is authorized by FDA. According to the FDA these vaccines have meet the criteria for emergency use authorization (EUA). However, (EUA) – is a short of full approval, thus, pharmaceutical companies needed submit a new request for the FDA to make the vaccine fully approved. It can also take time for a vaccine to be approved for worldwide use, although the pandemic situation is getting worse, especially in America. Additionally, new mutated COVID19 virus is can be seen on a regular basis which is alarming. Because it arises questions, such as authorized vaccine will enough to control pandemic and enough to fight new upcoming mutated viruses?

We are very aware of a deadly SARS CoV2 coronavirus mutation that has overtaken the world, causing enormous health and economic havoc to the new century.

Never the less, in order to contain the epidemic, we will need to sustain public health techniques such as physical distance, early warning, and self-isolation before adequate vaccinations are created to combat this disease.

Chapter 8

Conclusion

The growth of the COVID-19 vaccine has experienced significant obstacles in vaccine R&D. The planet is facing a public health crisis and economic tragedy, and one of the crucial solutions is to produce an effective and secure vaccine in the shortest time possible. We urgently need to develop an effective SARS-CoV-2 infection vaccine. So far, a number of pharmaceutical companies and academic institutions worldwide have launched their SARS-CoV-2 vaccine development programs. While it is understood that the creation of an effective vaccine is urgent, there are difficulties in research and development, as well as in policies aimed at developing precautionary and preparatory measures for the development and use of the SARS-CoV-2 vaccine. Reflecting closely, there are many cases of pandemics, such as the 1918 Spanish influenza pandemic, the most extreme pandemic in history, which spread over two years in three waves, affecting about one-third of the world's population and killing about 100 million citizens. In the absence of any definite drug, vaccination is necessary. While the production of vaccines appears to be attractive, it is anticipated to face many obstacles. Hope has been generated by the development of vaccine technologies, recent support pledges, regulatory facilitations, and the speed shown. The production of vaccines would be improved by a deeper understanding of pathophysiology, immunopathology, and an effective animal model. Although investments and initiatives for the production of vaccines are accelerated in view of the current pandemic magnitude and intensity, it may be difficult to retain momentum and pace of development once the episode subsides. We have to be patient enough to accept that there is a gap in virus knowledge. Like many other viruses, vaccine development efforts may not be successful, or we may have modestly effective vaccine development efforts.

8.1 Limitations

- The period of clinical trials is a considerable hindrance to the rapid development of vaccines. A vaccine agent must undergo at least three stages of placebo-controlled clinical testing, which can also take years to complete, to validate its efficacy and effectiveness. (Kaur & Gupta, 2020)
- The analysis was limited to only publications in the English language websites such as sciencedirect, pubmed and mendeley, which may have been a limiting factor since most of the early COVID-19 results came from studies focused in China. (Chakraborty & Parvez, 2020)
- No vigorous research is done about COVID-19, as a result most suitable vaccine yet to find. So, vaccine development is still undergoing process. Furthermore, few vaccines with 95% efficacy are being used in present days to fight and prevent transmission. However, these drugs/vaccines are not yet approved by FDA or WHO. Because, there is no adequate response data and post licensing data to prove that these vaccines are safe and will not affect our body in the long run. Additionally, there no data for special group of patients such as pregnant women, elderly patients, children, disease (heart problem) patients. (Chakraborty & Parvez, 2020)
- Finally, my data is based on still date, so more data is needed and hopefully in future more treatment and appropriate vaccines will be available in the future which will be suitable for all region (global population) people.

8.2 Recommendations

• Continuous progress through preclinical and clinical studies of candidate vaccines.

• Continuous, thorough characterization of COVID-19 immunopathogenesis.

• Execution of post-marketing broad monitoring systems to track the safety of SARS-CoV2 vaccines.

(Koirala et al., 2020)

8.3 Future aspects of this study

8.3.1 CTL peptide vaccine

Vaccine development primarily focused on expressing a host humoral immune response through vaccination with complete protein antigen. However, CLT peptides' vaccine can generate a Tcell response which is a significant alternative approach. The majority of vaccine stimulate humoral immune response; however, they do not deliver a robust T-cell response. (Herst et al., 2020)

8.3.2 B-cell engineering

To produce a safe, effective and long-lasting vaccine, an effective strategy can be targeting specific antigen in human with encoded antibodies. These encoded antibodies can be achieved by genome editing with the help of CRISPR/Cas9 technology. With this technology, substantial goal is to engineered genomes which can be updated and repurposed directly with improved and optimized

functions. Thus, it is hypothesized that a similar approach will be feasible for engineering human B-cells.

To this end, well-organized expression of particular antibodies can be accomplished in these cells under the guidance of endogenous regulatory elements responsible for antibody production. Vaccines cause B-cells to develop antibodies to specific pathogenic antigens (epitopes) (e.g., Sspike protein in SARS-CoV-2).-(Faiq, 2020).

8.3.3 Microneedle patches for vaccine delivery

As an alternate delivery route to improve the vaccine potency of the rich network of immunological antigen-presenting cells in the dermis and epidermis layers under the skin, microneedles were anticipated. Numerous studies have established the microneedle distribution parameters of a wide range of vaccines, demonstrating equivalent or higher immunogenicity to traditional intramuscular pathways, overall stability level and dose-saving benefits. In addition, recent analyses of the mechanism have been able to explain the biological processes underlying microneedle vaccination (Suh et al., 2014).

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