A Review on the Therapeutic Design and Challenges of Potential COVID-19 Vaccines

By
Name: Ahmed Ziad
ID: 16346038

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
Brac University
February 2021

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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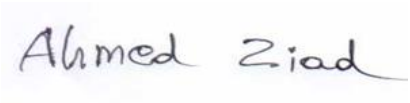

Ahmed Ziad

16346038

Approval

The thesis titled “A Review on the Therapeutic Design and Challenges on Potential COVID-19 Vaccines” submitted by Ahmed Ziad (16346038) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy.

Examining Committee:

Supervisor:

Dr. Md. Abul Kalam Azad

Assistant Professor, Department of Pharmacy

Brac University

Academic Coordinator:

Dr. Hasina Yasmin

Professor, Department of Pharmacy

Brac University

Departmental Head:

Dr. Eva Rahman Kabir

Professor, Department of Pharmacy

Brac University

Ethics Statement

This study does not involve any human and animal trial.

Abstract:

An unprecedented emerge of a rapid human-to-human transmissible respiratory illness, known as COVID-19 caused by the SARS-CoV-2, a novel coronavirus from December 2019, in Wuhan, China has changed the world drastically. Soon after its emergence the virus caused a serious health emergency that compelled the health officials to declare it an epidemic, followed by a global pandemic by the World Health Organization (WHO). In spite of some drug's improving results for treating the symptoms of COVID-19, it has been however recommended that only an effective vaccine can help get rid of this pandemic. In response to this pandemic an unbelievable effort has been observed to develop a vaccine due to the strong coordination and cooperation among the stakeholders, funders, vaccine developers, regulatory authorities, policy makers, governments etc. In this review the ongoing strategies for developing COVID-19 vaccines, some vaccine candidates and their pre- and post-development challenges have been comparatively analyzed.

Keywords: vaccine; vaccine candidates; coronavirus; COVID-19; treatments; challenges.

Dedication

Dedicated to my parents, grandparents and my project supervisor, Dr. Md. Abul Kalam Azad.

Acknowledgements

First of all, I would like to thank Almighty for his unlimited blessings in attempt to empower me with the strength and willingness to accomplish this project work.

I would like to express my sincere gratitude to my project and academic supervisor, Dr. Md. Abul Kalam Azad (Assistant Professor, Department of Pharmacy, Brac University) for his valuable supervision and enthusiasm throughout this project. He was genuinely a source of advice and support throughout my study and project writing. I am incredibly obliged for his precious feedback and suggestions throughout my research that helped me a lot to complete this project work smoothly.

I would also like to express my humble gratitude to Dr. Eva Rahman Kabir (Professor and Chairperson, Department of Pharmacy, Brac University) for her dedication, contribution and guidance towards the student as well as the department.

Finally, I would like to express my gratitude to my parents who keep inspiring me to go beyond my limits. I would not have come this far without their constant prayers and unconditional love. I would also like to thank all the people who, whenever needed, have helped me with their utmost abilities.

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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
ADE	Antibody Dependent Enhancement
MSC	Mesenchymal Stem Cell
COVAX	COVID-19 Vaccine Global Access
HLA	Human Leukocyte Antigen
VAERD	Vaccine Associated Enhanced Respiratory Disease
BCG	Bacille Calmette Guerin
HCT	Human Challenge Trial
CTL	Cytotoxic T Lymphocytes

Chapter 1

Introduction

1.1 Coronavirus

Coronaviruses belong to the family *Coronaviridae,* which includes a group of enveloped, positive-sensed, single-stranded RNA viruses. They are detrimental pathogens for human and vertebrates as they frequently infect respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and other wild animals. *Coronaviridae* consists of two subfamilies which are *Letovirinae* and *Orthocoronavirinae*. Within the *Orthocoronavirinae* subfamily, there are four genera which are: alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus. Alphacoronaviruses and betacoronaviruses are found in mammals, whereas gammacoronaviruses and deltacoronaviruses are found in birds (Banerjee et al., 2019). The genome of Coronaviruses (CoVs) is a single-stranded positive-sense RNA with 5′-cap structure and 3′-poly-A tail. Structurally, CoVs have non-segmented genomes that share a similar organization. For this reason, this is often estimated that two thirds of the genome contain two large overlapping open reading frames (ORF1a and ORF1b), which further translated into the pp1a and pp1ab replicase polyproteins (figure 1). The polyproteins are finally processed to generate 16 non-structural proteins, designated as nsp1~16 (Y. Chen et al., 2020). Many of these human and animal coronaviruses may have origins in a variety of bat species. With the implementation of next generation sequencing technology, an enormous number of novel coronaviruses have been identified till now (Fan et al., 2019).

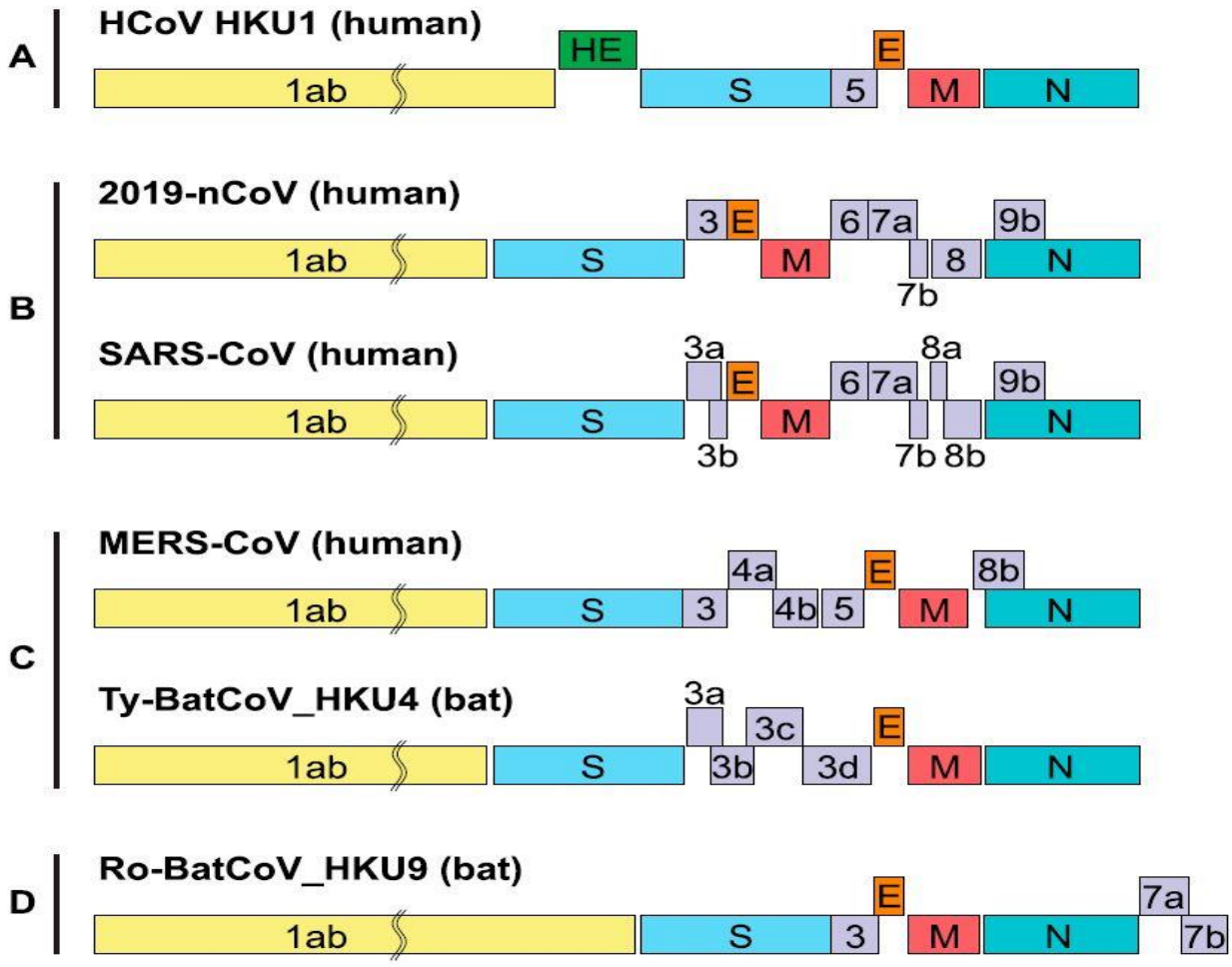

Figure 1: Betacoronavirus genome organization. Yellow boxes represent the 5'-untranslated regions (5'-UTR), open reading frame (orf), blue boxes showing the structural proteins including spike, orange boxes & red boxes are indicating envelop & membrane. Purple boxes are the accessory proteins. A to D are the examples of several betacoronaviruses includes human & bat coronavirus (adapted from Chan et al., 2020).

1.2 Evolution of the virus

Almost all early patients had animal exposure prior to disease development at the of the SARS epidemic. After the pathogen of SARS was identified, SARS-CoV antibodies were found in masked palm civets (*Paguma larvata*) and animal handlers in a remote market place. However, later, further investigations were done to clarify that SARS-CoV strains found in market civets those of which were transmitted to them by other animals. After this incident, two teams separately reported about the discovery of novel coronaviruses which was related to SARS-CoV and later on

designated as SARS-CoV-related viruses or SARS-like coronaviruses, in horseshoe bats (Cui et al., 2019). These findings indicate that bats are the natural hosts for SARS-CoV and civets were only intermediary hosts. Later, several SARS-CoV coronaviruses were found in bats (Shereen et al., 2020). A recent study has discovered that the co-existence of widely diverse SARS-CoV in bat populations is present in one cave of Yunnan province, China. This place later became a diversity hot spot, and the SARS-CoV in this place containing all the genetic variations found in other locations of China. In addition, all genetic elements that are needed to form SARS-CoV are found in the viral strains present at this site. The recombined virus infected civets and humans and adapted to these hosts before causing the SARS epidemic. It is proposed that Middle East Respiratory Syndrome coronavirus (MERS-CoV) are spilled over from bats to camels (figure 2). Progenitors of these viruses have recently been found in African bats, and the camelids are intermediate hosts of several other varieties which are also not harmful in humans and originated in rodents (Benvenuto et al., 2020).

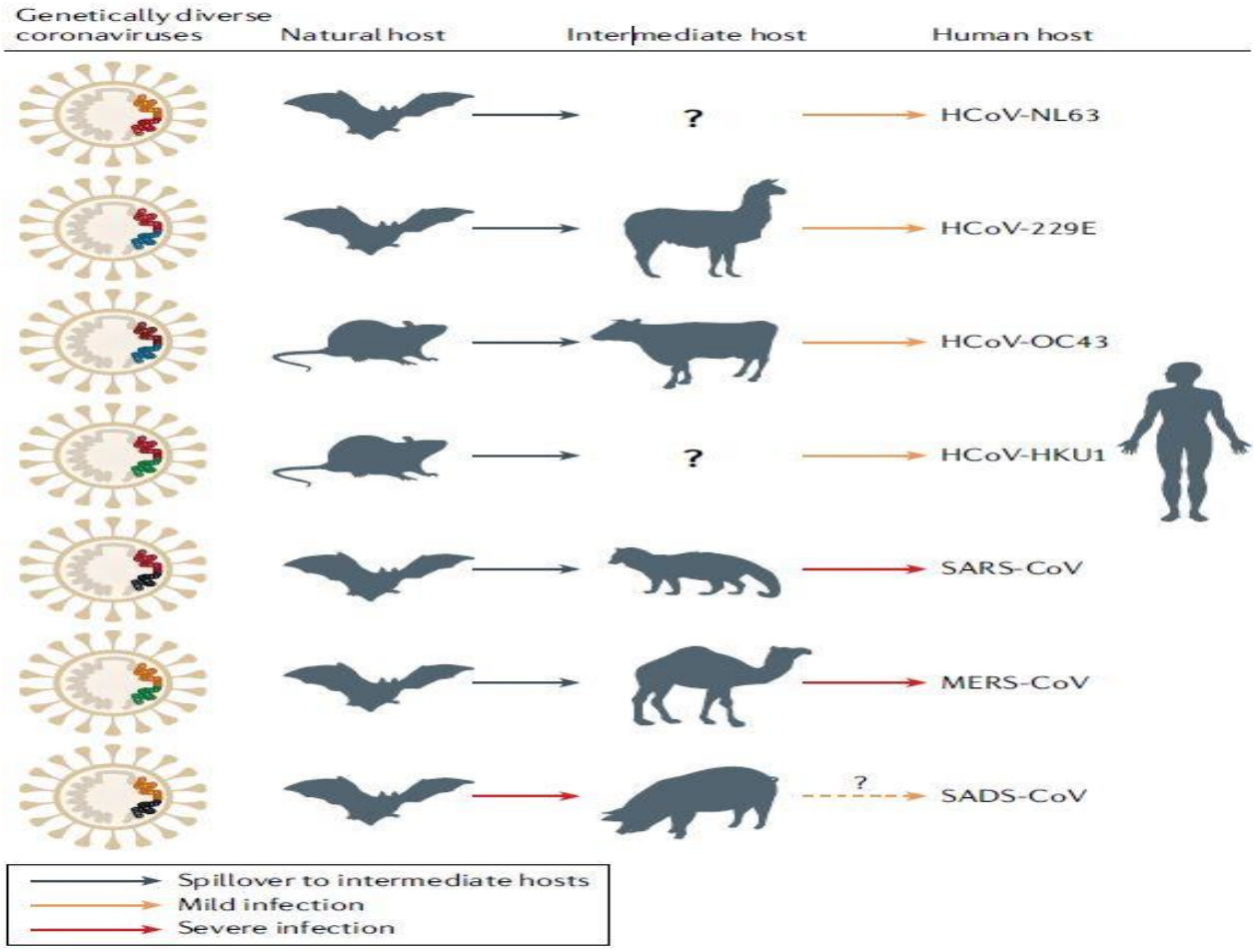

Figure 2: Animal origins of human coronaviruses. The solid arrows designate confirmed data whereas the broken arrows designate transmission between interspecies. The black arrows designate infection in the intermediate animals while the yellow arrows indicate mild infection in humans. The red arrows point out severe infections in humans or animals (adapted from Cui et al., 2019).

1.3 Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

After the sudden wide-spreading of the novel coronavirus, researchers sequenced and identified a new β-coronavirus, the genome of which has 86.9% identity to a previously published bat SARS-like CoV genome which is different from human SARS-CoV and MERS-CoV. Similar to individuals who were infected by SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, patients infected by SARS-CoV-2 showed a range of symptoms including dry cough, fever, headache, and pneumonia with an estimated mortality rate

ranging from 3 to 5% (Lan et al., 2020). Further analyses of the coronavirus genomes have revealed that SARS-CoV-2 is a member of the *Betacoronavirus* genus, which includes SARS-CoV, MERS-CoV, bat SARS-related coronaviruses (SARSr-CoV), as well as others identified in humans and animal species (Andersen et al., 2020).

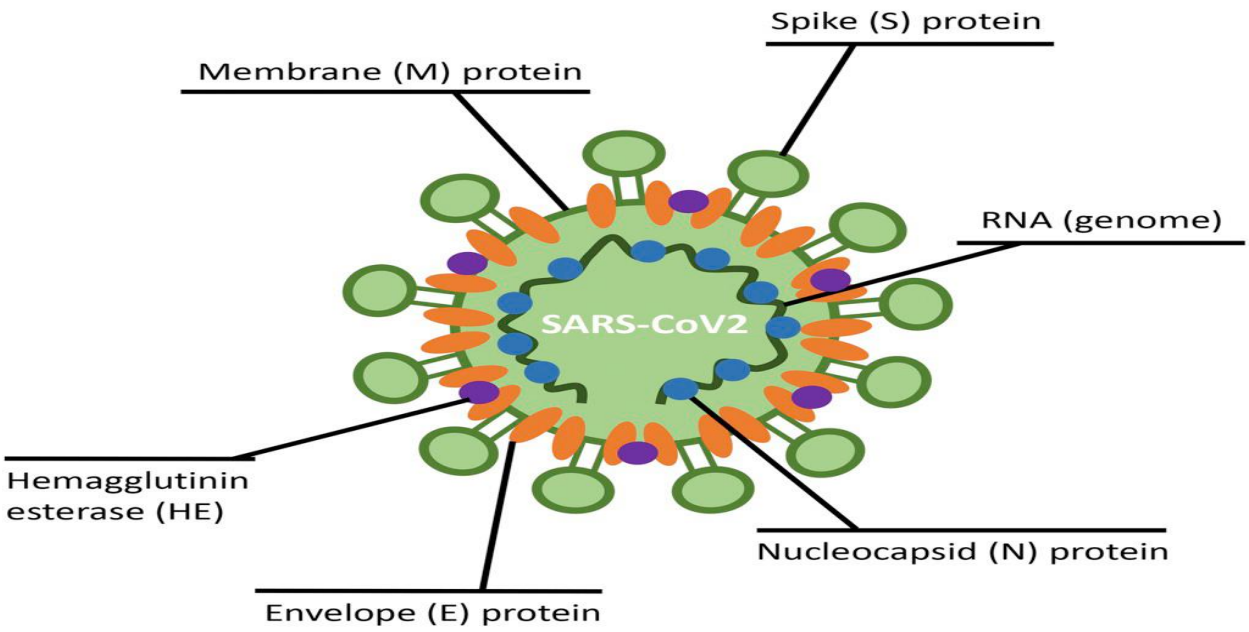

Figure 3: Structure of SARS-CoV-2. The spike protein (S) links to the trans-membrane ACE2 host receptor. The envelope (E) protein forms the viral envelope along with the membrane (M) protein and regulates its shape. Another cell entry pathway resembles the hemagglutinin esterase (HE) enzyme. Eventually, the protein nucleocapsid (N) is attached to the virus's RNA genome to form the nucleocapsid (copied from Felsenstein et al., 2020).

1.4 COVID-19

The disease caused by SARS-CoV-2 is known as Coronavirus disease 19 (COVID-19), since it has been detected since 2019. This disease is characterized by high fever, cough, sore throat, shortness of breath, fatigue, rhinorrhea and dyspnea (Yang et al., 2020). Comparing with general pneumonia, researchers found that these symptoms are not specific. The patients of SARS-CoV-2 infection show neurologic indicators like myalgia, dizziness, anosmia and ageusia. Some had digestive symptoms, such as diarrhea are also seen in some patients. Most of the patients on

admission presented with non-specific symptoms (Yang et al., 2020). The pregnant women infected SARS-CoV-2 had same symptoms as adult patients and one thirds of their neonates were infected with SARS-CoV-2. Some neonates and children had atypical symptoms which were later reviled. For the patients having renal problems, infected with SARS-CoV-2 had more proportion of moderate and severe disease. Renal transplantation recipients with COVID-19 appeared to have the most critical clinical outcomes (Yang et al., 2020).

1.5 Community Transmission of SARS-CoV-2

Based on the recent findings, it is proposed that COVID-19 transmits from human to human via direct, indirect (contaminated items or surfaces) or near contact through mouth and nose secretions with infected individuals. These involve saliva, or droplets of respiratory secretions or secretion. These are released when an infected person coughs, sneezes or speaks, from the mouth or nose. Near exposure with an infected person (in less than 1 meter) can cause other people to have COVID-19 when the droplets reach their mouth , nose or eyes (Cabore et al., 2020). Persons with the virus in their noses and throats will spread contaminated droplets, known as fomites, to objects and surfaces. By touching these items or surfaces and then touching their eyes, noses or mouths before washing their hands, other individuals may become infected. Some medical procedures may create very tiny droplets known as aerosols that can remain suspended in the air for longer periods of time. The novel coronavirus can be found in these aerosols. if people are not wearing personal protective equipment, these aerosols can potentially be inhaled by others. In some restricted settings, such as, nightclubs, restaurants, religious places or places where people meet regularly, several outbreaks of COVID-19 have been recorded recently. These routes of transmission by which the virus can spread are thought to be influenced by the socioecological context which influence the spread of disease. Some factors such as population density, population mobility,

weather, social behavior etc. can cause the virus to spread quickly. Finally, looking at vulnerability to SARS-CoV-2, it is proposed that older age, male sex and the presence of chronic comorbidities are related with further severe disease (Liu et al., 2020).

1.6 Necessity of vaccine

The quest for an effective medication against the virus or the resulting infection has been intense and has not led to any breakthrough agents. To stop this pandemic, we need a drug that is at least 95 percent successful against the disease but at this moment it seems quite difficult to develop such kind of drugs on a regular basis within a short period of time (Khuroo et al., 2020). Therefore, effective and safe vaccines shall be manufactured as soon as possible and made them available to all countries and populations affected by the pandemic at an affordable price. A vaccine has the power to generate herd immunity in the communities, which will reduce the spreading of disease, block transmission, and reduce the social and economic burden of the disease. Very high immunization coverage can effectively fight the pandemic, prevent secondary waves of infection, and control the seasonal endemic infection outbursts (Khuroo et al., 2020).

1.7 Objectives

- To study the status and ongoing strategies of COVID-19 vaccine development and
- To analyze some potential COVID-19 vaccine candidates and their pre and post development challenges.

Chapter 2

Pathophysiology and possible treatments

2.1 Pathogenesis of COVID-19

Clinical and immunological development shows that it is possible to split COVID-19 into 3 stages. Firstly, flu like illness with high viral load. After that it will turn out into critical phase which will decrease viral titres with accelerated inflammatory response and cause lung and other organ injury. Lastly, the last stage of the disease is characterized by fibrosis (Polak et al., 2020). In nasopharyngeal and endotracheal aspirate specimens, SARS-CoV-2 titers remain preeminent with symptoms throughout the whole first week, followed by a gradual decrease beginning at the end of the first week. There is less steep and constant drop in viral titers in patients with more serious diseases. During the process, it is recommended that the number of helper T-cells, T-cells and the memory helper T-cells be reduced. Persistent higher virus titers, poorly regulated by defective immune systems with higher levels of cytokines, point to the cumulative effect of cytopathic effects caused by the virus and injury mediated by immune effects. During the critical process, patients may succumb to illness or gradually recover. In different stages of disease, the choice of therapeutic agents varies. There are currently no reports of viral loads and cytokine concentrations in adolescents with COVID-19 (Dhochak et al., 2020).

2.2 Mechanism

When SARS-CoV-2 attacks cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 (figure 4), the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns along with ATP, nucleic acids and ASC oligomers (Joly et al., 2020). After the entry of the pathogen, it can undergo

several processes such as direct cytotoxic effects by binding with ACE2 receptors (figure 4 ①) and cause cell damages. In another way, after binding with the ACE2 receptor, this pathogen can cause serious dysregulation in the renin-angiotensin-aldosterone system (RAAS) which eventually occurs due to the downregulation of the ACE2 receptors (figure 4 ②). As a consequence, these leads to endothelial cell damage along with thrombo-inflammation and other complications (figure 4 ③). While the pathogen makes its entry inside the cell, it releases several components and these components are recognized by neighboring epithelial cells, endothelial cells and alveolar macrophages. They trigger the generation of various pro-inflammatory cytokines and chemokines. These proteins attract monocytes, macrophages and T cells to the site of infection, promoting dysregulated immune responses (figure 4). It may lead to further accumulation of immune cells in the lungs when a dysfunctional immune response occurs, causing overproduction of pro-inflammatory cytokines, thereby destroying the structure of the lungs. The resulting cytokine storm then circulates to other organs, resulting in multi-organ damage. Additionally, through antibody-dependent enhancement (ADE), non-neutralizing antibodies produced by B cells can increase SARS-CoV-2 infection, further boosting organ damage (Tay et al., 2020).

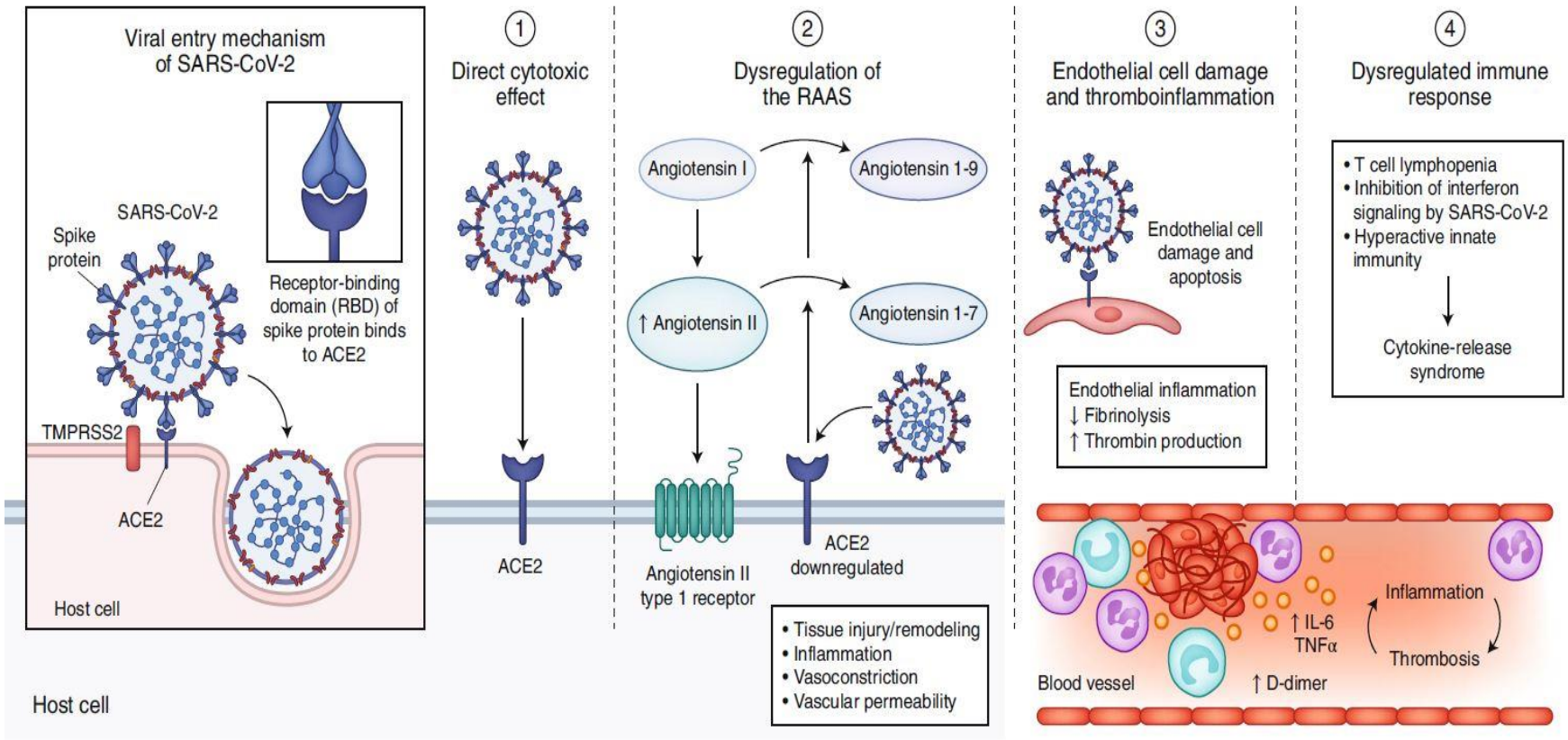

Figure 4: Sequence of events during SARS-CoV-2 infection. After the SARS-CoV-2 enters host cells through spike protein with the entry receptor ACE2 in presence of the TMPRSS2, (1) direct cell damage mediated by viruses occurs. then (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry occurs which leads to reduced cleavage of angiotensin I and angiotensin II hormone.(3) These lead to endothelial cell damage and thromboinflammation (4) finally, dysregulation of the immune response and hyperinflammation happens by inhibition of interferon signaling by the virus, T cell lymphodepletion (adapted from Gupta et al., 2020).

2.3 Possible treatment options

2.3.1 Antiviral agents

Remdesivir is a first developed investigational drug for the treatment of Ebola. It has extensively demonstrated pathways for overcoming drug resistance and genetic mutations in coronavirus. Remdesivir has demonstrated high in-vitro efficacy against SARS-CoV-2. In the United States, the first COVID-19 case was handled intravenously (IV) with remdesivir. Within 24 hours of remdesivir initiation, the patient became afebrile (Song et al., 2020). Similarly, the combination of lopinavir/ritonavir, which is indicated for HIV-1 treatment with other antiretroviral medicines, has increased growing interest in COVID-19 therapy. Lopinavir is a highly selective protease inhibitor for HIV-1 and HIV-2 while ritonavir raises the plasma concentration of lopinavir by inhibiting cytochrome P450. Given that clinical data on the efficacy and safety of the combination of lopinavir/ritonavir in COVID-19 patients is still limited and uncertain, further studies are needed to validate the potential function of these drugs. This combination is however commonly used in COVID-19 patients in Italy (Scavone et al., 2020). Comparably, Hydroxychloroquine and Chloroquine is also used for treating COVID-19. Chloroquine can inhibit SARS-CoV-2 entry and prevent virus-cell fusion by interfering with ACE2 receptor glycosylation and spike protein binding, indicating that chloroquine treatment may be more successful in the early stage of infection before COVID-19 decreases ACE2 expression and operation. There is some evidence that chloroquine and hydroxychloroquine could be capable of reducing cytokine. There is also evidence that zinc increases intracellular absorption of chloroquine (Wu et al., 2020). Recently, research findings by scientists from the German Primate Center (DPZ) suggested that there is no evidence of a strong antiviral activity or clinical benefit of chloroquine. Later, it was also discovered that chloroquine does not inhibit infection of human lung cells with SARS-CoV-2

(Hoffmann et al., 2020). Another effective drug is Ivermectin, a derivative of avermectin B, is a wide-spectrum microfilaricidal agent that is effective orally. Ivermectin prevents the chemical transmission over the nerve synapses that use glutamate-gated anion channels. Rapid stimulation of γ-aminobutyric acid (GABA) release from presynaptic nerve endings and improvement of the binding to the postsynaptic receptors accomplishes this. It does not affect synapses gated by other transmitter substances. This results in an increase in the permeability of the cell membrane to chloride ions resulting in hyper-polarization of the cell, which leads to paralysis and eventually the death of the parasite. Recent research on ivermectin against SARS-CoV-2 under in-vitro conditions revealed it could inhibit viral replication (Şimşek Yavuz & Ünal, 2020). A double-blind, placebo-controlled, randomized trial was performed for assessing the rapidity of viral clearance and safety of ivermectin among adult patients infected with SARS-CoV-2. During the study, 58 of the 22 patients received oral administration of 12 milligrams of ivermectin for 5 days. In the RTPCR test, 77 percent of patients who took Ivermectin tested negative for the disease within 14 days (Ahmed et al., 2021). Ribavirin has a proven history of use for nCoV in emergency clinical management plans (Khalili et al., 2020). Few researches on the treatment of coronaviruses have indicated this clinical utility during the SARS-CoV outbreaks in China and North America, and MERS-CoV outbreaks in the Middle East and Asia (Khalili et al., 2020). Moreover, recombinant interferons were used with varying results in the SARS and MERS patients (Felsenstein et al., 2020). Recently, two other drugs are currently evaluated in patients with COVID-19 which are camostat mesilate and nafamostat. These drugs are synthetic protease inhibitors of trypsin, prostasin, matriptase and plasma kallikrein. In Japan, they are approved for the treatment of chronic pancreatitis and post-operational reflux esophagitis (Scavone et al., 2020). The function of hypercoagulable state that leads to micro and macro-vascular thrombosis in

COVID-19 has received considerable attention. Patients who received anticoagulants had a reduced mortality rate. Heparin has anti-inflammatory effects, and can also inhibit viral attachment via SARS-CoV-2 surface receptor (Spike) S1 conformation changes (Wu et al., 2020). In addition, the use of bradykinin receptor B1 and B2 antagonists may be a novel strategy to treat the bradykinin-dependent local lung angioedema caused by COVID-19. This pathway may be indirectly responsive to anti-inflammatory agents or neutralizing strategies for anti-S-antibody-induced effects (Pascarella et al., 2020). Recently, Germany has announced that they will now use new antibody-based drug for treating the COVID-19 patients. Basically, it is two lab-made antibody cocktails known as REGN-COV2. It is suggested that these antibodies work as a passive vaccination (Weinreich et al., 2020).

2.3.2 Mesenchymal Stem Cell Therapy

COVID-19 can cause an overreaction of the immune system in the body to destruction. In COVID-19 patients, the immune system generates significant quantities of inflammatory factors in an overproduction of immune cells and cytokines, triggering a cytokine storm. Here the concept of mesenchymal stem cell (MSC) therapy in treating COVID-19 patients starts. Possibly, MSC therapy can stop the storm release of cytokines by the immune system and promote endogenous repair by reparative properties of the stem cells. Following intravenous injection, part of the MSC population falls into the lung, which is also regarded as a weakness of systemic infusion. But here these MSCs may restore the pulmonary microenvironment, protect alveolar epithelial cells, intercept pulmonary fibrosis, and cure lung dysfunction and COVID-19 pneumonia. It thus seems that MSC-based therapy could be an suitable candidate for clinical trials or at least a combination of treatment for COVID-19 patients (Golchin et al., 2020).

2.3.3 Convalescent plasma transfusion

Immune plasma refers to plasma that is gathered from individuals following infection resolution and antibody production. Passive antibody therapy may stop clinical infection or blunt clinical severity in novel coronavirus exposure in individuals through transfusion of convalescent plasma (Rajendran et al., 2020). Anecdotal use in patients suffering from SARS, MERS, Ebola and Influenza confirms its use as a neutralizing and/or immunomodulating agent. A wider randomized controlled study of the use of hyperimmune intravenous immunoglobulin for extreme influenza and Ebola found this technique not to be superior to placebo (Bloch et al., 2020). These studies indicate for broader use of COVID-19 convalescent plasma. After all, while evidence supports the safety and potential usefulness of convalescent plasma, randomized trials are required (Bloch et al., 2020).

2.4 Preventive measure: vaccines

As discussed before though several drugs are available in the market, they are only able to reduce the effectiveness of the disease. Several researches are continuing their trials about the effectiveness of many other drugs but only a vaccine can help eradicate this disease. Without any appropriate and effective COVID-19 vaccine the threat of new outbreak remains authentic as we have been seeing during the second wave all over the world. The protein structure of SARS-CoV-2 spike protein has been discovered. This should allow the rapid development and assessment of medical defensive measures to address the ongoing public health crisis. These results deliver the foundation for more research to improve vaccination strategy for this arising infection. Most vaccines produced for coronaviruses are targeted at the spike glycoprotein. The development of vaccine is a very elongated process, and unfortunately no vaccines are available to fight against this pandemic outbreak. Luckily, on 24 February 2020, Moderna company announced that the

experimental mRNA COVID-19 vaccine (also known as mRNA-1273), is ready for human testing (Zhai et al., 2020). At present, there are several biotechnology companies and universities in various countries working on to develop a SARS-CoV-2 vaccine. Developing the vaccine within a short period of time, which can usually take an average of 1.5 to 3.0 years, is often a skillful, crucial and demanding task (Badgujar et al., 2020). International cooperation is key to accelerating progress and must focus on manufacturing and logistical capacity preparation, as well as the conditions for making these technologies affordable and accessible to people around the world (Organisation for Economic Co-operation and Development, 2020). Several renowned companies such as Pfizer/Biontech, Moderna, AstraZeneca, Johnson & Johnsons etc. have already shown outstanding results by developing vaccine. Moreover, these companies are already proved safety issues as their candidates are doing good results in the clinical trials. The strategies of the candidates will be discussed briefly in the next chapters.

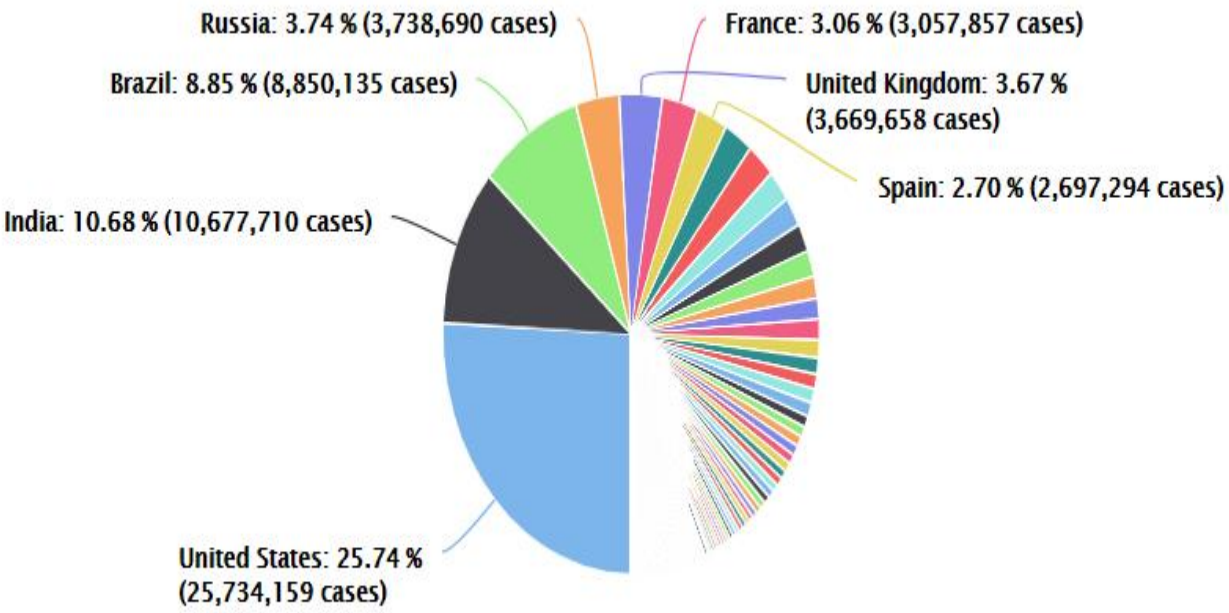

Figure 5: Current distribution cases (Worldometer, 25.01.2021)

Chapter 3

Vaccine strategies

3.1 Principle

A vaccine works by preparing the immune system to fight against pathogens such as viruses or bacteria. Pathogenic molecules (known as antigen) which are present in viruses and bacteria are the main factor for triggering the immune system. Our immune system can easily gain the process to identify them as unfriendly intruders by inoculating these antigens inside the body, generate antibodies and remember them for the future (Centers for Disease Control, 2018). Our immune system identifies the antigens immediately when the bacteria or virus reemerges and aggressively attacks them long before the pathogen can spread and induce illness. Vaccines are preparations of viruses or viral subunits that are weakened or killed which cause specific protective immunity. Vaccination is the single most effective method for preventing communicable diseases, demonstrated by the successes of the eradication programs for smallpox and poliomyelitis. A vaccine can produce herd immunity among population, which will diminish disease incidence, prevent transmission and minimize the disease's social and economic burden. Very high levels of immunization can effectively tackle the pandemic, avoid secondary infection outbreaks and control outbursts of seasonal endemic infections. By mimicking an infection, vaccines help to establish immunity. However, this kind of infection almost never causes sickness, but it causes T-lymphocytes and antibodies to be produced by the immune system. Sometimes, an artificial infection may cause mild symptoms, such as fever, after obtaining a vaccine. As immunity builds up in the body, these slight indications are common and can be presumed to. By mimicking an infection, vaccines help to establish immunity. This type of infection, however, almost never induces disease, but it stimulates the production of T-lymphocytes by the immune system and once

the fake infection is gone, the body is left with a supply of T-lymphocytes, as well as B-lymphocytes that will know how to combat this disease in the future. Even so, it normally takes the body a couple of weeks to produce T and B lymphocytes after vaccinations. A individual infected with any disease can also be able to grow indications and become ill before or after vaccination, as the vaccine did not have enough time to ensure protection (Burns et al., 2007).

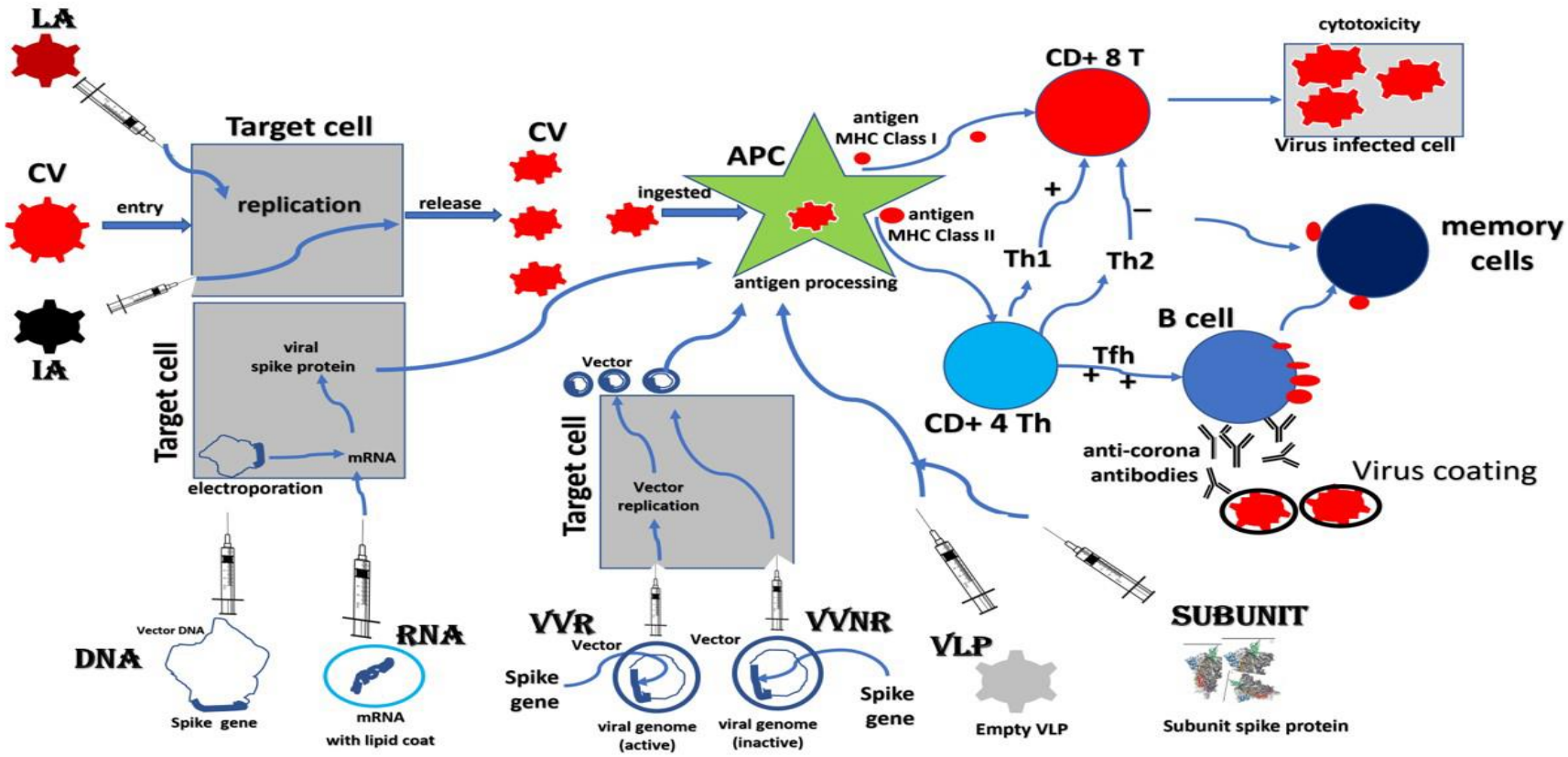

Figure 6: Vaccine methodology. Visual illustration of 8 system strategies for the production of COVID-19 vaccines and the mechanism followed to induce immune response of T cells and B cells. Live-attenuated vaccine (LA), inactivated vaccine (IA), DNA vaccine (DNA), RNA vaccine (RNA), viral vector replicating vaccine (VVR), non-replicating viral vector (VVNR), virus-like particles (VLP) and subunit vaccine (Subunit) are techniques. CV indicates coronavirus while APC indicates cell processing antigen (copied from Khuroo et al., 2020).

3.2 Vaccine components

An adjuvant is a substance which helps with the vaccination process by raising vaccine immunogenicity. This is always a required addition since an antigen's purification can lead to the loss of its intrinsic adjuvant properties. Adjuvants are also currently the area of significant concern with respect to the safety of vaccines, with mercury-based (thiomersal) adjuvants increasingly eliminated, and now questions about aluminum-based adjuvants (without any clear basis) are increasing. Many vaccines contain aluminium salts such as aluminium hydroxide, aluminium phosphate or potassium aluminium sulphate. They act as adjuvants, enhancing and prolonging vaccine immune response. In certain live vaccines, gelatin extracted from pigs is used as a stabilizer to protect live viruses against temperature damage. In vaccines, gelatin is highly processed and hydrolyzed which are broken down by water, thereby separating from the normal gelatin used in foods (Bastola et al., 2017). Active ingredients contain parts of viruses or bacteria known as antigen. Vaccines contain tiny quantities of active ingredients which can be just a few micrograms (millionths of a gram) per vaccine. Some vaccines contain whole bacteria or viruses. In these cases, the bacteria or viruses will either be severely weakened (attenuated) so that they cannot cause disease in healthy people, or killed altogether (inactivated). Many vaccines contain only parts of viruses or bacteria, usually proteins or sugars from the surface. These stimulate the immune system but cannot cause disease (Eagle & Gad, 2014). For the delivery of vaccines, it is important that in many of them there are preservative agents. This ensures immunogenicity and overall efficacy of the vaccine. This also increases the vaccine's shelf-life, this is especially important in the latest work on flu virus vaccines, as a dose usually only lasts one year (Barbara E Eldred, Angela J Dean, 2006). Like sugar or gelatin, stabilizers help vaccine active ingredients continue to function while the vaccine is being produced, processed, and transported. Owing to

something like a temperature change where the vaccine is kept, they prevent the active ingredients in vaccines from shifting (Eagle & Gad, 2014).

3.3 Vaccine development during the SARS-CoV-2 pandemic

Within weeks of discovering and sequencing the novel coronavirus, scientists jumped into research on SARS-CoV-2 vaccines. Several factors such as basic scientific understanding, including in areas of structural biology as well as genomics and supporting a new era in vaccine development, established vaccine platforms and newly developed ones, vaccine research against other two coronaviruses which are designated as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) viruses—that, however, vaccine testing experiences during the recent epidemics which are Ebola (occurred in 2014-2016) and Zika (occurred in 2015-2016), did not go above phase I studies (Kieny & Salama, 2017). At present, several candidates for the SARS-CoV-2 vaccine are in the pipeline, some have already reached phase I or I-II clinical trials and a few candidates started phase III trials. Moreover, some of them are already in production stage. While shortcuts in the production and testing of vaccines could accelerate the pace of scientific advancement, they could also lead to compromises in safety, acceptability and ethics (Grady et al., 2020).

3.4 Types of vaccines

Live attenuated vaccines

Live vaccines are made using ‘wild’ viruses or bacteria that have been attenuated, or weakened, until introducing into the vaccine. The weakened vaccine viruses or bacteria replicate (grow) inside the vaccinated individual after immunization (figure 6). Normally it is milder than 'wild' disease when a live attenuated vaccine induces 'disease,' e.g., chickenpox vaccine. Live attenuated

injection vaccines usually become effective after one dose. Those administered orally typically require three doses, however. If given to a person with an impaired response to the immune system, such as leukemia or HIV infection, or taking immunosuppressive medication, the administration of a live attenuated vaccine may trigger severe illness as a result of uncontrolled replication (growth) of the vaccine virus. Vaccines that are live attenuated include rotavirus, BCG, chickenpox, and measles, mumps, and rubella (Baxter, 2007).

Inactivated vaccines

These vaccines are developed by inactivation or killing of the pathogen during the vaccine making process. A proven example of this vaccine is the inactivated polio vaccine. This strategy requires that in cell culture or other flexible medium such as hens eggs, the virus will spread to a higher titer in which the virus can be effectively and entirely inactivated using agents like formaldehyde or B-propiolactone without compromising immunogenicity. From an industrialization perspective, the immunogenic dose is low to moderate in terms of virus yield (in 10 m). This strategy has had outstanding vaccine achievements such as inactivated polio vaccine (IPV), hepatitis A (HAV), and influenza (Centers for Disease Control, 2018).

Toxoids vaccines

Some bacterial diseases aren't caused directly by a bacterium itself, but by a bacterium-produced toxin. One example is tetanus: its symptoms are not caused by *Clostridium tetani*, but by the neurotoxin which it produces known as tetanospasmin. Immunizations can be made for this form of pathogen by inactivating the toxin which causes symptoms of disease. As with organisms or viruses employed in killed or inactivated vaccines, this can be achieved through treatment with

chemicals such as formalin, or through the use of heat or other means. Immunizations produced by inactivated toxins are known as toxoids (Baxter, 2007).

Subunit vaccines

Subunits or single proteins that are prepared in cell culture uses recombinant DNA methods and fermentation processes. This method can work well where immunity can be given by a single protein and where the expression system requires the viral protein to be folded and processed appropriately. For coronaviruses, subunit vaccines depend on eliciting an immune response to the S-spike protein to prevent its binding with the host ACE2 receptor. Various protein subunit vaccines are successfully formulated against several pathogens like influenza virus, hepatitis B, pneumonia and meningitis etc (Badgujar et al., 2020).

Conjugate vaccines

These vaccines fight against a different kind of pathogen. These bacteria consisting antigens called polysaccharides, having an outer layer of sugar-like substances. This form of coating masks the antigen which makes it difficult for the immature immune system of a young child to recognize it and respond to it. For these types of bacteria, conjugate vaccines are successful because they bind the polysaccharides with antigens and therefore, the immune system responds very well to. This association allows the immature immune system to respond to the coating and establish an immune response. An example of such a vaccine is the type B (Hib) Haemophilus influenzae vaccine (Centers for Disease Control, 2018).

Others

Recombinant vaccines are made using bacterial or yeast cells to manufacture the vaccine. A small piece of DNA is taken from the virus or bacterium against which need to be protected. This is inserted into other cells to make them produce large quantities of active ingredient for the vaccine. For example, to make the hepatitis B vaccine, part of the DNA from the hepatitis B virus is inserted into the DNA of yeast cells. These yeast cells are then able to produce one of the surface proteins from the hepatitis B virus, and this is purified and used as the active ingredient in the vaccine. In case of vectored or chimeric virus approaches, this is where the current virus vaccine may be genetically engineered to contain genes encoding foreign virus antigens. The chimeric vaccine should maintain parent vaccine strain attenuation and growth characteristics but promote immunity against foreign virus. In case of naked DNA, this is where a DNA encoding viral antigens plus suitable control sequences for expression are administered directly to the receiver. DNA expression contributes to an immune reaction against the encoded antigens (Badgujar et al., 2020).

3.5 Clinical trials

Every new vaccine has to be absolutely safe. Any possibility of side effects may call a halt to development or cause the vaccine to be withdrawn, according to the 'precautionary principle.' The cost of producing a single candidate vaccine is rising at about 12 percent per annum and is now approaching almost $1bn. It usually takes an average of 15 years to develop a new vaccine. Presumably, vaccines can have long-lived protection after a single dose, and be easy to produce on a wide scale. Every new vaccine follows a strict R&D protocol which must be followed and completed carefully before it is approved for marketing. Regulatory agencies, including the WHO, the U.S. Food and Drug Administration (USFDA), the European Medicines Agency (EMA), and

national authorities in several countries have released guidelines connected to vaccine clinical assessment. The vaccine development standards are tighter than those designed for drug development. As the vaccines are being developed for global use, they have tremendous development and marketing potential. The production of vaccines are followed with a particular step-by-step process and is generally divided into several phases including exploratory, preclinical, clinical and post-marketing. There are three phases in the clinical phase: Phases I, II and III. After successful clinical trials, there are two regulatory approvals required before the clinical stage, involving 'Clinical Trial Authorization' to allow 'first-in-human' testing and 'Biologic License Application/Approval' for the vaccines promotion (Olszewska et al., 2006).

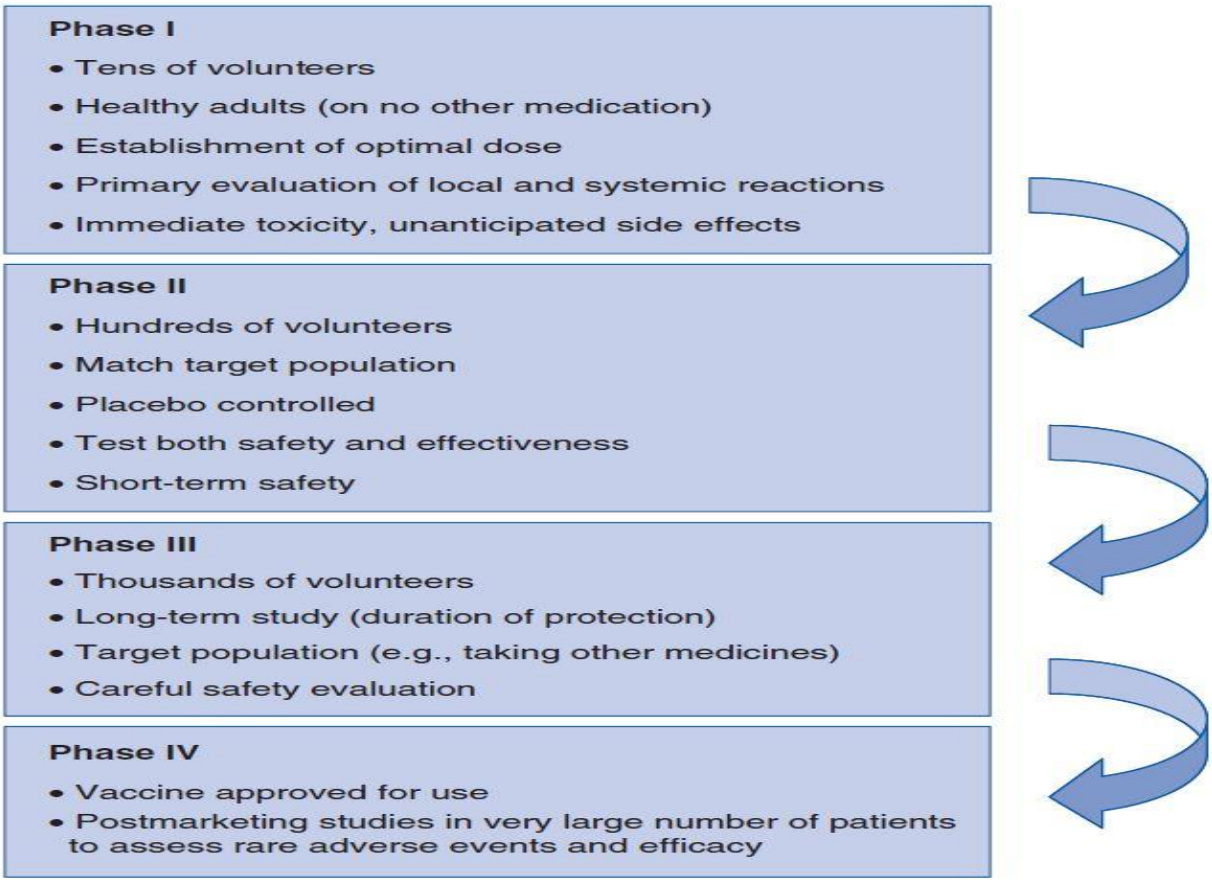

Figure 7: Procedure of clinical testing of a potential vaccine

3.6 Advantages of vaccine over other medications

Vaccines are particularly important for the prevention or elimination of infectious diseases. The World Health Organization estimates that the measles vaccine has saved more than 20 million deaths since 2000. Vaccinations have a major impact on disease and virus control in the US and around the world. Immunizations have turned lethal, crippling diseases into entirely avoidable and life-threatening diseases. When more people have vaccinations, it makes everyone less likely to get the disease that is being vaccinated against This disease control is called herd immunity and benefits the whole community (Nandi & Shet, 2020). Effectiveness of the vaccine refers to the immediate protection provided to individuals under suitable conditions and usually focuses on preventing clinically obvious consequences (e.g., meningitis, hospitalization, death). Where a contagious agent may cause a variety of different clinical expressions, the primary assessment will focus on one particular clinical manifestation (for example, pneumococcal invasive disease during a pneumococcal vaccine study) whereas the secondary examination may involve other clinical manifestations as data sources. Immunizations protect us from serious diseases and also prevent such diseases from spreading to others. Immunizations have over the years prevented epidemics of one-time prevalent infectious diseases such as mumps, measles and whooping cough. We have seen the near eradication of others like the deadly smallpox and polio, because of immunizations. Over the past two decades as pressure has mounted on public health budgets, more advanced (and expensive) vaccines have become available, health economic evaluation has become an important feature of programmed immunization planning. Lastly, vaccines are safe and secure. All vaccines are subject to long and thorough examination by scientists, physicians and the federal government to ensure they are safe (Doherty et al., 2016).

Chapter 4

Vaccine candidates for COVID-19

The majority of COVID-19 vaccine manufacturing operations are in North America. There may be differences in COVID-19 epidemiology in different geographical areas. In order to monitor the pandemic effectively, large-scale involvement and participation of the other countries in the southern hemisphere is needed for research and development to produce an effective COVID-19 vaccine. The Coalition for Epidemic Preparedness Innovations (CEPI) is working with global health authorities and vaccine developers to support the development of vaccines against COVID-19. As China was the first to map the genome sequence of the novel coronavirus immediately after the SARS-CoV-2 epidemic, China has a head start on developing a COVID-19 vaccine. China has initiated phase II clinical trials with their vaccine candidates for a COVID-19 vaccine. China's CanSino Bio and its collaborators at the Academy of Military Medical Sciences Institute of Biotechnology were the first of COVID-19 vaccine developers to join phase II trials, just three weeks after the Phase 1 study (Nagarajan et al., 2020). Several nations have recently been engaged in negotiations to potentially participate in COVID-19 Vaccines Global Access (COVAX), a global effort intended at partnering with vaccine manufacturers to provide countries worldwide with equal access to safe and reliable vaccines once they are licensed and accepted. COVAX currently has the largest and most diverse COVID-19 vaccine portfolio in the world, including nine candidate vaccines, nine more under review and continuing negotiations with other major manufacturers (Dr Seth Berkley, 2020).

Table 1: Current vaccine candidates (adapted from World Health Organization (WHO), 2020)

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/regulatory status-Coronavirus candidate
Non-Replicating Viral Vector	Recombinant adenovirus expressing Trunctuated S protein (rADV-S)	International Vaccine Institute (IVI)	SARS	Phase I-II
Replicating Viral Vector	Recombinant measles virus Spike protein	University Health Network, Canada; Center for Disease Control and Prevention (CDC)	SARS	Pre-Clinical
Replicating Viral Vector	MV-SARS recombinant measles virus vaccine expressing SARS CoV antigen	Institut Pasteur	SARS	Phase I
Protein Subunit	SARS recombinant spike protein plus delta inulin	Vaxine Pty Ltd, Australia	SARS	Pre-Clinical
Virus-like Particle	SARS VLPs S protein and influenza M1 protein	Novavax	SARS	Phase III
DNA	DNA prime–protein S437–459 and M1–20	Institute of ImmunoBiology, Shanghai Medical College of Fudan University, China	SARS	Pre-Clinical
DNA	DNA vaccine VRC-SRSDNA015-00-VP; Biojector used	National Institute of Allergy and Infectious Diseases (NIAID)	SARS	Phase I
Non-Replicating Viral Vector	Heterologous Adenoviral prime boost AdHu5 s AdC7-nS	University of Manitoba; University of Pennsylvania School of Medicine; Southern Research Institute; Fox Chase Cancer Institute	SARS	Phase II-III
Non-Replicating Viral Vector	VEEV replicon particles expressing the SARS-CoV S	University of North Carolina at Chapel Hill, USA	SARS	Pre-Clinical
Non-Replicating Viral Vector	Recombinant DI expressing S protein	National Institute of Infectious Diseases, Japan	SARS	Pre-Clinical

Protein Subunit	Recombinant trunctuated S-N fusion protein	Beijing Institute of Genomics, China	SARS	Phase II-III
Protein Subunit	Recombinant TM-truncated S protein	Chinese Center for Disease Control and Prevention; Canadian Science Centre for Human and Animal Health	SARS	Phase I
Protein Subunit	Trimeric Spike protein	HKU-Pasteur Research Centre; The University of Hong Kong; National Institutes of Health; Centers for Disease Control and Prevention; CombinatorX	SARS	Pre-Clinical
Virus-like Particle	Chimeric VLP (S protein SARS plus E, M and N proteins of mouse hepatitis virus)	University of Texas Medical Branch (UTMB)	SARS	Pre-Clinical
Inactivated Virus	purified inactivated Vero-cell SARS vaccine	Institute of Microbiology and Epidemiology, National Vaccine and Serum Institute; Beijing Genomics Institute (BGI); Harbin Institute of Veterinary Medicine	SARS	Pre-Clinical
Inactivated Virus	β-propiolactone inactivated virus vaccine	National Institute of Allergy and Infectious Diseases (NIAID); University of Virginia	SARS	Pre-Clinical
Live Attenuated Virus	Live attenuated SARS-CoV MA-ΔExoN	University of North Carolina	SARS	Pre-Clinical
Inactivated Virus	ISCV	Sinovac Biotech Ltd (/Beijing Kexing Bio-product), Chinese Centre for Disease Control and Prevention; Chinese Academy of Medical Sciences	SARS	Phase I
Inactivated Viral Vector	RABV-SARS	Thomas Jefferson University	SARS	Pre-Clinical
Inactivated Virus	whole virus	Sanofi	SARS	Phase I-II

4.1 Prominent vaccine candidates

4.1.1 BioNTech/Pfizer

Type of vaccine: 3 LNP-mRNAs

Basically, under the joint efforts of Pfizer and BioNTech, four candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) are in production stage and each candidate represents a particular combination of messenger RNA (mRNA) type and target antigen. Both BNT162b1 and BNT162b2 are nucleoside-modified RNAs, formed in lipid nanoparticles. BNT162b1 encodes an evolved SARS-CoV-2 receptor-binding domain antigen (RBD) whereas BNT162b2 encodes an optimized full-length SARS-CoV-2 spike protein antigen. Each mRNA format is combined with a formulated lipid nanoparticle (LNP). Two of the candidates contain the bigger spike sequence, whereas the smaller optimized receptor binding domain (RBD) from the spike protein is included with the other two candidates. Two of the four candidates of the vaccine use a nucleoside-modified mRNA (modRNA), one includes a uridine that contains mRNA (uRNA), and the fourth candidate for the vaccine includes self-amplifying mRNA (saRNA). Each mRNA design is combined with a formulated lipid nanoparticle (LNP). (Genetic Engineering & Biotechnology News, 2020). The preliminary phase I/II results of approximately 120 patients for BNT162b2 showed a more favorable overall tolerability profile than BNT162b1, with no severe adverse effects and usually mild to moderate and intermittent systemic effects such as fever, exhaustion, and chills. The phase II/III trial is planned to test two BNT162b2 in up to 30,000 participants aged 18–85, at about 120 sites worldwide including in regions with substantial predicted transmission of SARS-CoV-2. Participants will be randomized 1:1, vaccine candidate to placebo in an observer-blinded study whose primary endpoints will be COVID-19 prevention in those who were not infected with

SARS-CoV-2 prior to immunization, and COVID-19 prevention regardless of whether participants were previously infected with SARS-CoV-2 (BioNTech, 2020).

The protocol of its phase I / II / III trial of the BNT162 vaccine program has recently been publicly published by Pfizer. There were 15 participants in each phase I group (12 receiving an active vaccine and 3 receiving a placebo). Thirteen groups were analyzed in this process, corresponding to 195 participants in total. 21,999 vaccine recipients were included in the chosen phase II/III vaccine candidate, BNT162b2, at a dose of 30 μg. A minimum of 40 percent of participants are projected to be in the > 55-year. Placebo was given to an equal number of participants in a 1:1 ratio. In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and more than 16 years of age), the study will test a 2-dose (separated by 21 days) regimen of various different dose levels of 2 investigational RNA vaccine candidates for successful immunization against COVID-19. There will be 44,000 participants in the Pfizer study (Pfizer, 2020). The vaccine is found 95 percent effective against COVID-19. The vaccine reached all primary endpoints of effectiveness, with a greater than 30 percent likelihood of true vaccine efficacy of more than 99.99 percent. These findings met our stated performance criteria, which greatly exceeded the minimum FDA authorization criteria (Polack et al., 2020).

The first Emergency Use Authorization (EUA) was issued by the U.S Food and Drug Administration (FDA) for a vaccine for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older on December 11, 2020. The emergency usage authorization facilitates the distribution of the Pfizer-BioNTech COVID-19 Vaccine in the USA (U.S. Food & Drug Administration, 2020). The vaccine has been approved by Canada's health regulator, the day after the UK became the first country in the world to approve it. Moreover, Switzerland, Malaysia, Bahrain & Mexico have issued EUA for using this vaccine (The Indian Express, 2020).

4.1.2 University of Oxford/AstraZeneca

Type of vaccine: ChAdOx1-S

ChAdOx1 nCoV-19 is a chimpanzee (Ch) adenovirus-vectored vaccine (Ad), whose development was led by the University of Oxford (Ox). The blueprint of the initial ChAdOx1 vaccine was first originated during the development of ChAdOx1 MERS vaccine back in 2019. The vaccine ChAdOx1 MERS is composed of the replication-deficient simian adenovirus vector ChAdOx1, which contains the protein antigen MERS Spike. While it was first induced to rhesus macaques (species of monkey), it shows seroconversion rapidly after a single intramuscular vaccination. The vaccine protected against respiratory disease and pneumonia, and reduced the viral load by many orders of magnitude in lung tissue. MERS-CoV replication of the ChAdOx1 MERS vaccinated animals in type I and type II pneumocytes was missing. In rhesus macaque, a single vaccination with ChAdOx1 MERS results in protection against disease progression and virus replication associated with MERS-CoV challenge, and a prime-boost regimen further decreases viral replication. In addition, ChAdOx1 MERS vaccination has been covered from a number of concurrent MERS-CoV strains in mice (van Doremalen, Haddock, et al., 2020). Since then, during the recent pandemic, scientists begin to analyze with ChAdOx1-S and eventually comes out with the promising ChAdOx1 nCoV-19. It has been shown to stimulate an immune response to SARS-CoV-2. It is also known as AZD1222. This vaccine is produced within three months by the scientists at Oxford University's Jenner Institute. British-Swedish multinational pharmaceutical and biopharmaceutical company AstraZeneca has signed an agreement in partnership with the University of Oxford to produce and distribute the vaccine. For better understanding, an experiment was conducted where mouse strains (BALB/c, and outbred CD1) were vaccinated with ChAdOx1 nCoV-19 for observing humoral and cellular immune responses (figure 8). After some

days, Total IgG titers were detected against spike protein subunits in all vaccinated mice (Figure 1a). In addition, Virus-specific neutralizing antibodies were found in all mice which were vaccinated with the vaccine but no neutralization was found from mice vaccinated with the same vaccine (Figure 1b). T-cell responses measured by IFN-γ ELISpot and intracellular cytokine staining (ICS) were found in spleen (Figure 1c). Finally, a strong Th1-type response was detected post vaccination as supported by high levels of IFN-γ and TNF-α, and low levels of IL-4 and IL-10 (Figure 1d).

The vaccine was genetically modified using adenovirus, and combined with the SARS-CoV-2 spike protein genetic material. AZD1222 is made from a virus (ChAdOx1), which is a weakened form of a common cold virus (adenovirus) that causes chimpanzee infections, has been genetically changed so that it is almost impossible to grow it in humans. Spike glycoprotein has been added to produce this vaccine which is used to create proteins from coronavirus SARS-CoV-2. This protein is normally present on the SARS-CoV-2 surface, and plays a key role in the SARS-CoV-2 virus infection pathway. Latest researches have shown that the SARS-CoV-2 uses its spike protein to bind to ACE2 receptors (present in human cell) to enter the cells and cause infection. After the ChAdOx1 nCoV-19 vaccine has been introduced, human body can recognize and develop an immune response to the Spike protein which may help stop the SARS-CoV-2 virus from entering human cells and thus prevent infection. The coronavirus DNA is then "expressed" when these ChAdOx1 particles enter human cells, creating the spike protein for the immune system to respond. The viral vector can't replicate and cause a continuous infection, which is vital for vaccine safety (Mullard, 2020).

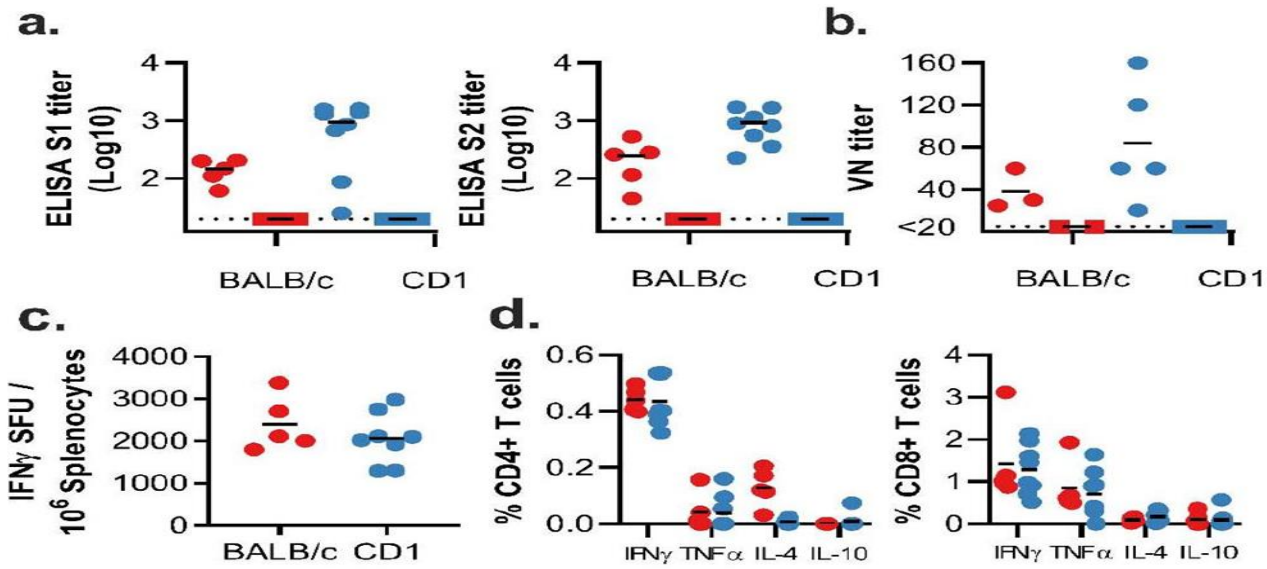

Figure 8: Humoral and cellular immune responses to ChAdOx1 nCoV-19 vaccination in mice. a. End point titer of serum IgG detected against S1 or S2 protein. Control mice were below the limit of detection. b. Virus neutralizing titer in serum. c. Summed IFN-γ ELISpot responses in splenocytes toward peptides spanning the spike protein. Control mice had low (<100 SFU) or no detectable response. d. Summed frequency of spike-specific cytokine positive CD4+ or CD8+ T cells. BALB/c = red; CD1 = blue; vaccinated = circle; control = square; dotted line = limit of detection; line = mean; SFU = spot-forming units (modified from van Doremalen, Lambe, et al., 2020).

Starting in April 2020, 1,077 participants (aged between 18–55 years) were recruited to conduct phase I/II trials. Participants were assigned randomly to obtain either the vaccine ChAdOx1 nCoV-19 or an approved vaccine (MenACWY) that is used as a 'control' for comparison. The dose used in this trial was selected based on personal experience with other vaccines based on ChAdOx1 and the recombinant adenovirus for ChAdOx1 nCoV-19 was administered at a dose of 5×10^{10} viral particles. Severity adverse events were graded and Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay to count antigen-specific T cells. Preliminary trial results clearly indicate that the vaccine can cause an antibody response within 28 days. This reaction is close to that of individuals who have recovered from COVID-19, allowing the vaccine to protect most people from infection. Ten volunteers each received a second "booster" dose of the vaccine. This increased the response of the antibody to even higher levels, and in a

laboratory setting 100 percent of blood samples from this group showed neutralizing activity against COVID-19 infection (University Of Oxford, 2020). The vaccine also induced T-cells which specifically recognize SARS-CoV-2, the COVID-19-causing virus. It is promising to see both antibody and T cell responses, as this together is the right kind of immune response that may contribute to virus defense. Importantly, the vaccine displays a suitable safety profile, with no significant adverse effects caused by the vaccine (Folegatti et al., 2020). The early findings of this first-in-human clinical trial have enabled the continuation of drug research into phase II and III trials. Older age groups with comorbidities, health care workers and those with a higher risk of exposure to SARS-CoV-2 are recruited and evaluated for the effectiveness, safety and immunogenicity of ChAdOx1 nCoV-19 given as a single-dose or two-dose administration regimen in further trials conducted in the UK and overseas. Phase III trials were conducted in Brazil, South Africa and the United Kingdom (Mahase, 2020).

In the midst of news that doses could be ready by 28 December, the Oxford/AstraZeneca coronavirus vaccine is now in production stage. Trial results show that when a full dose is given followed by another full dose, the vaccine has 62 percent efficacy. During the last week of December, the Medicines and Healthcare Products Regulatory Agency (MHRA) of UK is expected to give the vaccine the green light. Complications surrounding the findings of the initial trial, unveiled last month by the University of Oxford, seem to be responsible for the delay. The government formally ordered the medicines regulators to determine the suitability of the Oxford/AstraZeneca vaccine for temporary supply as soon as the company submits the required data on safety, consistency and efficacy (The Guardian, 2020).

4.1.3 Sinovac

Type of vaccine: Inactivated

This vaccine is also known as CoronaVac (formerly PiCoVacc), and is based on an inactivated pathogen. It is composed of a SARS-CoV-2 inactivated type, developed by Sinovac Biotech, China. This vaccine has been used extensively in 3 animal models. This animal model uses rats, mice, and rhesus macaques (a species of monkey) that demonstrate immune response activation in all models. The developed neutralizing antibodies are able to fight off infection in response to SARS-CoV-2. In the phase I/II trial this vaccine shows promising results. The clinical trials of phase I/II were constructed as randomized, double-blind, and placebo-controlled trials. A total of 743 healthy volunteers, aged between 18 and 59, participated in the trials. There were 143 volunteers in phase I, and 600 in phase II. No significant adverse events were reported in either the phase I or phase II studies. The findings of phase II clinical trials show that the vaccine produces neutralizing antibodies with a 0 to 14-day period after 14 days of the vaccination. The seroconversion rate of the neutralizing antibody is above 90%, which indicates that the candidate of the vaccine will cause a positive immune response (Xu et al., 2020). The phase III trial was carried out in brazil.

In the midst of phase III trials, Brazilian officials announced in October that the vaccine was effective. The death of a participant in the phase III trial in October, however, prompted the Brazilian authorities to temporarily suspend the Sinovac trial. On the other hand, the first government approval of a Sinovac vaccine was released by the United Arab Emirates, claiming preliminary data revealing that it was 86 percent successful (The New York Times, 2020). The vaccine candidate for Sinovac Biotech Ltd. was approved for emergency use in July as part of a

program in China to vaccinate high-risk groups such as medical personnel, frontline employees, etc (Daily Sabah, 2020).

4.1.4 Moderna/National Institute of Allergy and Infectious Diseases (NIAID)

Type of vaccine: LNP-encapsulated mRNA

Known as mRNA-1273, it is a SARS-CoV-2 prefusion stabilized protein mRNA vaccine selected by Moderna in collaboration with researchers from the National Institute of Allergy and Infectious Diseases (NIAID). The first clinical sample, sponsored by the Alliance for Advances in Outbreak Preparedness, was completed on February, 2020 and underwent analytical testing. On March, 63 days from sequence selection to phase 1 research dosing, the first participant in the NIAID-led phase 1 analysis of mRNA-1273 was dosed. It is an encapsulated Novel Lipid Nanoparticle (LNP) mRNA vaccine encoding for a stable prefusion shape of the Spike protein. mRNA is a single-stranded molecule carrying genetic code from the DNA in the nucleus of a cell to ribosomes, the protein-making machinery of a cell. Also known as mRNA-1273, Moderna, Inc. uses the virus sequence to develop its mRNA vaccines, not through working on the virus itself. This mRNA platform offers major advantages over fundamental research, manufacturing, and clinical development in speed and performance. The vaccine codes for the spike protein when it is injected into human body. Thus, even without the introduction into the body of an attenuated (recognizable but not harmful) virus, the body knows what the virus looks like and prepares itself with the antibodies necessary to function against it (Hussey et al., 2020). Researchers recently published a preclinical study which showed that mRNA-1273 protected mice from SARS-CoV-2 infection. mRNA-1273 produced neutralizing antibodies in mice when administered as two 1-microgram (mcg) intramuscular injections dose, three weeks apart. Mice which are given two 1 mcg injections

and subsequently challenged with SARS-CoV-2 virus 5 or 13 weeks after the second injection, were covered against viral replication in the lungs and nose (Corbett et al., 2020). It also induced strong CD8 T-cell responses in mice but did not induce the type of cellular immune response connected to vaccine-associated enhanced respiratory disease (VAERD). Moreover, mice were challenged 7 weeks after just one dose of 1 mcg or 10 mcg of mRNA-1273 were also shielded from viral replication in the lung. Based on Phase 1 results, the Phase 2 analysis will be adjusted to research two levels of dose, 50 μg and 100 μg, in order to choose a dose for pivotal studies (Jackson et al., 2020).

Recently, following demands for more accountability, Moderna has been the first organization to publish the full blueprints of its studies. A randomized and placebo-controlled phase III study was performed by Moderna to determine the vaccine 's efficacy, safety, and immunogenicity. Another essential aim of this research is to carry out additional studies to support the understanding of SARS-CoV-2 and COVID-19 infections. Participants were randomly allocated to receive either 100 μg mRNA-1273 vaccine injections or placebo control at a randomization ratio of 1:1. In accordance with the procedure, Good Clinical Practice (GCP), and all relevant regulatory criteria, this study was carried out. nearly 30,000 participants who were 18 years of age or older at the time of approval were enrolled. For each participant, the study period will be approximately 26 months. This involves a screening period of up to 1 month and a 25-month study period covering the first dose on Day 1 and the second dose on Day 29. The last scheduled visit of the participant will take place on Day 759 (Month 25), 24 months after the second dose on Day 29 (Month 1). The conclusion of the analysis will be the last planned visit by the last participant on Day 759 (Month 25). The research started in late July, indicating that the first interim analysis would not take place until late December and the final analysis would take place in late May (ModernaTX, 2020).

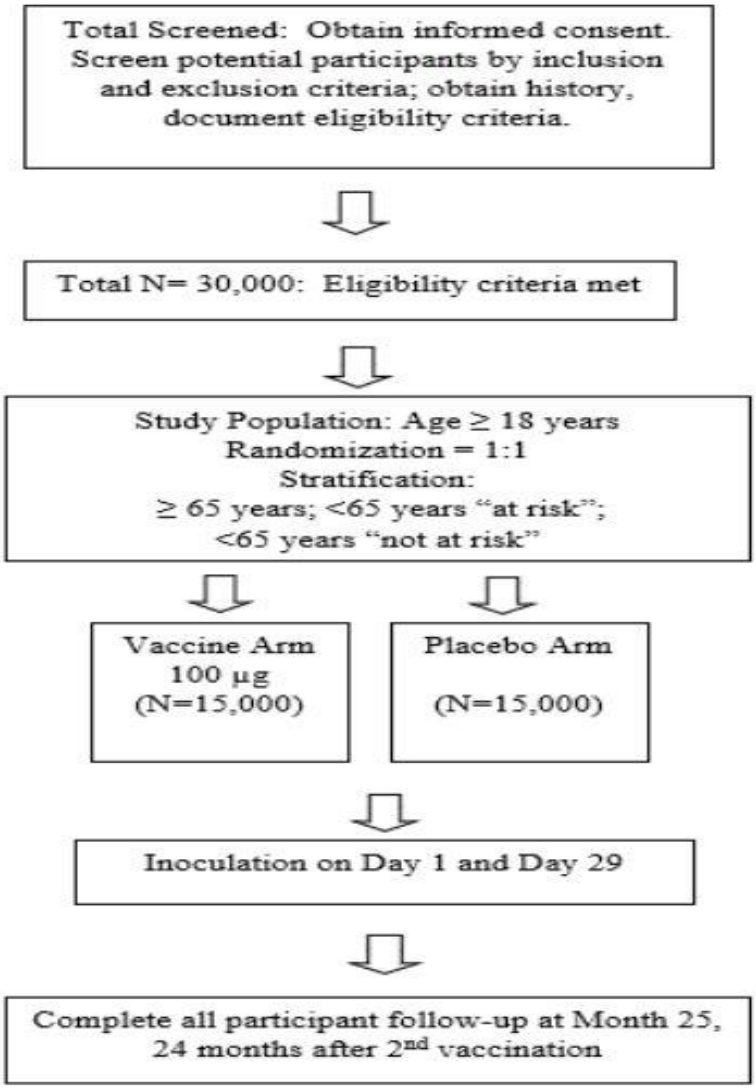

Figure 9: Study Flow Diagram of mRNA-1273. N indicates number of studies (copied from ModernaTX, 2020)

The primary efficacy findings from Phase III COVID-19 vaccine trial have been published by Moderna. The two-dose regimen of the vaccine is 94.1 percent effective against SARS-CoV-2, according to the data (Baden et al., 2020). Furthermore, The Food and Drug Administration (FDA) has approved Moderna's vaccine for emergency use starting from December 18, 2020 which allows millions more doses to be shipped across the country. A fast and complex push to administer some 5.9 million doses of the Moderna vaccine throughout USA starts with the emergency authorization.

Moderna intends to submit a Biologics License Application for full U.S. licensure in 2021 (Moderna Press release, 2020).

4.1.5 CanSino Biological Inc./Beijing Institute of Biotechnology

Type of vaccine: Adenovirus Type 5 Vector

This vaccine uses a new and modified common cold virus to bring genetic material into the human body from the novel coronavirus, a process also used in the Oxford/AstraZeneca vaccine. It is a vaccine for recombinant novel coronavirus disease (Type 5 Vector Adenovirus). Ad5-nCoV is a genetically engineered vaccine candidate with type 5 replication-defective adenovirus as the vector for expressing the spike protein of SARS-CoV-2, which is intended to be used to avoid the disease caused by the novel coronavirus infection. The first to be studied in humans is the new Ad5 vector COVID-19 vaccine assessed in the Phase I trial. It uses a weakened common cold virus (adenovirus, which readily infects human cells but is unable to trigger disease) to transmit genetic material to the cells that codes for the spike protein SARS-CoV-2. Then these cells generate the spike protein and move to the lymph nodes where the immune system produces antibodies that recognize the spike protein and combat the coronavirus (Purba & Harahap, 2019). A randomized, double-blind, placebo-controlled phase II clinical trial was performed in Adults Aged Over 18 years to test the safety and immunogenicity of the vaccine. This phase II clinical trial is structured to determine the immunogenicity and safety of Ad5-nCoV encoding for a full-length SARS-CoV-2 spike (S) protein. It was examined in a single center in Wuhan, China, in 508 healthy adults. Both doses of the vaccine tested in the trial induced neutralizing response of the antibody to SARS-CoV-2, the virus that causes COVID-19. This involves 85 percent of participants developing novel coronavirus antibodies and a T-cell response within 14 days of receiving the injection. The shot

also appeared safe and secure, although adverse reactions were recorded by 72-74 per cent of participants in both dosage classes. Severe adverse effects were less frequent, however, with just 9% in the dose group of 1×1011 viral particles and one participant in the dose group of 5×1010 viral particles having a significant side effect (Zhu et al., 2020).

For the country's military, the Chinese government has approved the use Cansino's Covid-19 vaccine. In a statement, Cansino announced that on June 25, the Chinese Central Military Commission had released a "military specially-needed drug approval" for the vaccine. Special approval shall last for a period of one year and shall apply only to military personnel. They also reported that their patent application for the COVID-19 vaccine was accepted by government officials, marking the first and only patent issued so far by the Chinese authorities for the COVID-19 vaccine (CNN Health, 2020).

4.1.6 Wuhan Institute of Biological Products/Beijing Institute of Biological Products/Sinopharm

Type of vaccine: Inactivated

Known as BBIBP-Cor, when induced it can produce high-level neutralizing antibodies that can block the virus from infecting monkeys, rats, guinea pigs and rabbits. In mice, scientists detected neutralizing antibodies that could block the virus from infecting host cells in all animals at three different dose levels after immunization with the vaccine. But a three-dose regimen's immunogenicity was higher than that of both the one- and two-dose systems. Two-dose immunizations using 2 μg/dose protected against SARS-CoV-2 intratracheal challenges in rhesus macaques, without observable antibody-dependent infection enhancement. Furthermore, BBIBP-CorV showed efficiency and strong genetic stability for vaccine manufacturing and the results

support earlier evaluations of BBIBP-CorV during clinical trials (Wang et al., 2020). A phase I/II trial with 1,120 people was performed with BBIBP-CorV vaccine. In June, the China National Biotech Group (CNBG) reported some interim results showing positive antibody responses but no information on adverse effects. It has been confirmed that adverse effects of inactivated vaccine would be lower than other vaccines which is usually expected from an inactivated vaccine. Phase 3 trial in Abu Dhabi, United Arab Emirates (UAE) is currently under way. Sinopharm is evaluating the potential vaccine in the United Arab Emirates in a phase III trial which is planned to recruit 15,000 participants, since China has too few new cases to be a suitable test site (REUTERS, 2020).

The United Arab Emirates recently reported that 86 percent efficacy was observed in clinical trials of Sinopharm's vaccine. In a couple of countries, this vaccine has been approved for emergency use and the company has performed late-stage clinical trials in 10 countries including Argentina, the UAE and Morocco. It has also been studied in Peru, but due to a serious adverse event that took place with one of the study volunteers, confirmed by the Peruvian government, the country suspended the tests (The Guardian, 2020).

4.1.7 Inovio Pharmaceuticals/International Vaccine Institute

Type of vaccine: DNA plasmid vaccine with electroporation

Known as INO-4800, it is a DNA vaccine candidate linked to the SARS-CoV-2 coronavirus. This is the only nucleic acid-based vaccine that remains stable for more than a year at room temperature and does not need to be frozen during transport or storage for years. This phenomenon is very essential considerations in the fight against the current pandemic when introducing mass immunizations. The vaccine INO-4800 is consist of the plasmid pGX9501, which encodes SARS-CoV-2 for the full length of the Spike glycoprotein. It is a synthetic DNA-based vaccine that is

highly susceptible to enhance developmental timelines due to the ability to rapidly design multiple candidates for preclinical research, flexible manufacturing of the drug product in large quantities, and the possibility to exploit proven regulatory pathways to the clinic. Synthetic DNA is temperature-stable and free from cold chains, which are essential features for resource-limited delivery (Smith et al., 2020). Human clinical trials started on April with forty healthy adult volunteers in Pennsylvania University (Philadelphia) and Kansas City, (Pharmaceutical Research Centre), where screening of potential participants has already begun. This is an open-label trial to determine INO-4800's efficacy, tolerability, and immunological profile administered by intradermal injection. At Week 6, 94 per cent of participants in the phase I study exhibited overall immune responses after two doses of INO-4800 in preliminary experiments with forty volunteers. The INO-4800 protocol was deemed secure and well tolerated with no significant adverse effects through Week 8. In addition to the promising interim phase I results reported on 30 June 2020, it has been shown that INO-4800 protects mice in SARS-CoV-2 viral challenge studies, where INO-4800 vaccination prevented viral replication in the lungs of animals challenged with SARS-CoV-2. Phase II / III trials are expected to be carried out soon (INOVIO, 2020).

4.1.8 Johnson & Johnson (J&J)/Janssen Pharmaceutical Companies

Type of vaccine: Monovalent vaccine composed of a recombinant adenovirus type 26 (Ad26) vector

In partnership with Beth Israel Deaconess Medical Center, part of Harvard Medical School, Johnson and Johnson (J&J) and Janssen Pharmaceutical research teams developed and tested several vaccine candidates using Janssen AdVac technology and selected their leading recombinant vaccine candidate Ad26COVS1 for the prevention of coronavirus infection. The AdVac technology works to mimic elements of a pathogen by using an adenovirus as a vector of

the genetic code of an antigen. The body produces both a long-lasting humoral and cellular immune response against the antigen when encountering the antigens, by developing immune cells and antibodies. In the future, the body will be able to react quicker and more efficiently if the body meets the actual pathogen, as immune cells and pathogen-specific antibodies are quickly produced in the body (Janssen Pharmaceutical, 2020). The phase I/II research was recently announced by J&J to assess the efficacy, reactogenicity and immunogenicity of the SARS-CoV-2 investigational vaccine, Ad26COVS1, recombinant, in 1,045 healthy adults 18 to 55 years of age and adults 65 years of age and older. The research was conducted in the United States and Belgium. J&J declared the start of its large-scale, pivotal, multi-country phase III trial for its COVID-19 vaccine candidate, on September 2020. To determine the effectiveness and safety of the vaccine for the prevention of COVID-19, a randomized and placebo-controlled phase III study was performed. This is a phase III, pivotal efficacy and safety research, multicenter, randomized, placebo-controlled, in adults between the ages of 18 and 60. Overall, this study was randomly allocating an approximately 60,000 adults. The sample size takes into account the uncertainty of the epidemiological situation in conjunction with the ability to have a high likelihood (about 90 percent) of hitting a time to signal for a vaccine with an expected 60 percent vaccine efficacy within 8 months of the analysis. Up to 60,000 volunteers across 3 continents participated in the trial to study the safety and effectiveness of a single vaccine dose against placebo in preventing COVID-19 (Vaccines, 2020). J&J stated that they anticipate the first batches of a COVID-19 vaccine could be available for emergency use authorization in early 2021.

4.1.9 Novavax

Type of vaccine: Prefusion protein made using Novavax's recombinant protein nanoparticle technology

Also known as NVX-CoV2373, it is a vaccine candidate developed from the SARS-CoV-2 genetic sequence. It was developed to produce antigen derived from the coronavirus spike protein using Novavax recombinant nanoparticle technology and contains Novavax proprietary saponin-based Matrix-M adjuvant to boost immune response and induce high levels of neutralizing antibodies. NVX-CoV2373 contains distilled protein antigens and is neither capable of replicating nor of triggering COVID-19. In preclinical trials, an indication of antibodies that inhibit the binding of spike protein to virus-targeted receptors, a crucial aspect of successful vaccine safety, has been shown. It was relatively well tolerated and elicited strong antibody responses superior to those seen in human convalescent sera in the trials. Two ongoing phase II studies are also evaluating NVX-CoV2373 (Taylor et al., 2020). In collaboration with the U.K., the first phase III analysis of this candidate is being carried out in the United Kingdom's government taskforce on vaccinations. It is estimated that the study will recruit 10,000 patients between the ages of 18 and 84. Half of the participants will receive two intramuscular vaccine injections consisting of 5 μg of protein antigen with 50 μg of Matrix-M adjuvant, provided 21 days apart, whereas placebo will be offered to half of the study participants (BioSpace, 2020). Recently, the company has published the phase III trial reports where it says 89.3% vaccine efficacy was observed. Moreover, this percentage was observed against the new variant of coronavirus strain of UK. Efficacy against the original SARS-CoV-2 strain was calculated to be 95.6% (NOVAVAX Press Release, 2021).

4.1.10 Gamaleya National Center of Epidemiology and Microbiology

Type of vaccine: Common adenovirus modified to carry genes for the "spike" protein

The Russian government has approved a COVID-19 vaccine for widespread use despite it apparently undergoing only a phase I trial. The Russian vaccine has been developed by the Gamaleya Institute, Moscow, and uses two human adenovirus vectors and the SARS-CoV-2 spike protein to produce an immune response. Named as Sputnik V, it uses a weakened virus to deliver small parts of a pathogen and stimulate an immune response which is a vector vaccine based on adenovirus DNA. Adenovirus is basically used as a "container" to deliver the coronavirus gene to cells, starting the synthesis of the envelope proteins of the new coronavirus "introducing" the immune system to a potential enemy. phase I and II clinical trials of the vaccine have been completed on August 1, 2020. The vaccine elicited powerful antibody and cellular immune response from. Not one single person in the current clinical trials became infected with COVID-19 after being given the vaccine. High-precision studies for antibodies in the blood serum of volunteers have confirmed the high efficacy of the vaccine. A variety of countries will enter Sputnik V's clinical trials locally, such as the UAE, Saudi Arabia, the Philippines and possibly India or Brazil. The vaccine is scheduled to start mass production in September 2020 (Sputnik V, 2020). The key concern is that a phase III clinical trial has not yet been performed into the Russian vaccine. Such a trial, usually involving more than 10,000 volunteers, and comparing the vaccine to placebo, will aim to demonstrate both vaccine effectiveness and safety. It is not sure whether the Russian vaccine will protect people against SARS-CoV-2 without phase III results. Efficacy statements are currently based on preliminary evidence from two limited phase II studies, details of which are summarized in a vaccine website funded by the Russian direct investment fund, which reports that all 76 volunteers receiving the vaccine developed high levels of SARS-CoV-2 specific

antibodies and strong cellular immunity.4 However, as it remains unknown who has received it (Caddy, 2020).

In August, the vaccine received limited approval in Russia, before phase III trials had even begun. Published findings from small early-stage studies showed in September that Sputnik V triggered an immune response. Russia faced global outrage from tens of thousands of individuals for authorizing a vaccine that has not completed advanced trials, and experts both at home and abroad cautioned against its widespread use before the tests were finished (Associated Press, 2020).

4.2 BCG vaccination against SARS-CoV-2

The Bacille Calmette-Guerin (BCG) is a live bacterial attenuated vaccine that is given to people to protect against Tuberculosis. Recent research shows that in countries where BGC vaccine is implemented as a compulsory pediatric vaccine, the number of positive cases and COVID-19 mortality rates are poor relative to countries that do not require the BCG vaccine. Numerous countries are currently performing phase II/III trials of the BCG vaccine to test its efficacy as a preventive human vaccine to be safe from COVID-19. The University of Melbourne and Murdoch Children's Research Institute, Australia are involved in a randomized, controlled, Phase 3 trial and the Netherlands Radboud University Medical Center are also involved in a Phase 3 BCG CORONA randomized parallel assignment trial (Nagarajan et al., 2020). The BCG vaccine could improve the ability of the immune system to combat pathogens, including the coronavirus. Several studies have shown that in humans and mice the BCG vaccine may protects against viral infections that affect the respiratory tract. BCG vaccination allows our immune system to combat infection by viruses. There is also a pathway by which the vaccine prevents and decreases the risk of harmful contagious diseases. Additional researches have confirmed that BCG vaccine enhances resistance to other viruses in laboratory animals which indicates that it can be used as a possible treatment

tool for COVID-19. In countries that did not follow BCG vaccination, such as the USA, Italy , Spain, France , Germany, South Korea, Iran, etc., COVID-19 spread rapidly on those areas, while the countries that had previously adopted BCG vaccination showed a relatively slow spread and low magnitude of COVID-19 (Aaron Miller, 2019).

As shown in figure 10, it indicates a strong and significant correlations between COVID-19 outcomes and the number of years of BCG administration. Because of varying stages of the pandemic in each country, a unified aligned key date of a country was defined as the first date when DPM reached for the first time the DPM value of 0.5 or higher. A strong negative correlation was observed with Deaths Per Million (DPM) outcome where linear regression (R) = -0.48 (p-value = 0.00056) and -0.47 (p-value = 0.00084) when aligned at DPM threshold of 0.5 and 2, respectively (figure 10 a & b). Similarly, for the Cases Per Million (CPM) as COVID-19 outcome, a similar trend with R = -0.38 (p-value = 0.0091) and -0.35 (p-value = 0.017) was observed (figure 10 c & d). The analysis was performed 20 days following two different alignments of key dates.

The BCG vaccine is usually used internationally (except in the United States, Germany, Spain, Italy, etc.) to prevent TB infection. Researchers have recorded that there are ten times higher severe COVID-19 infections and elevated fatalities in countries without mandatory BCG vaccination systems. Five clinical trials have begun using the BCG vaccine as a therapeutic medication for COVID-19 in healthcare workers and the elderly population in different countries. According to the relevant evidence, the BCG vaccine will help reduce the incidence of COVID-19 infection with lower morbidity and mortality and could become a game-changer to avoid the spread of the pandemic of COVID-19 (Sharma et al., 2020).

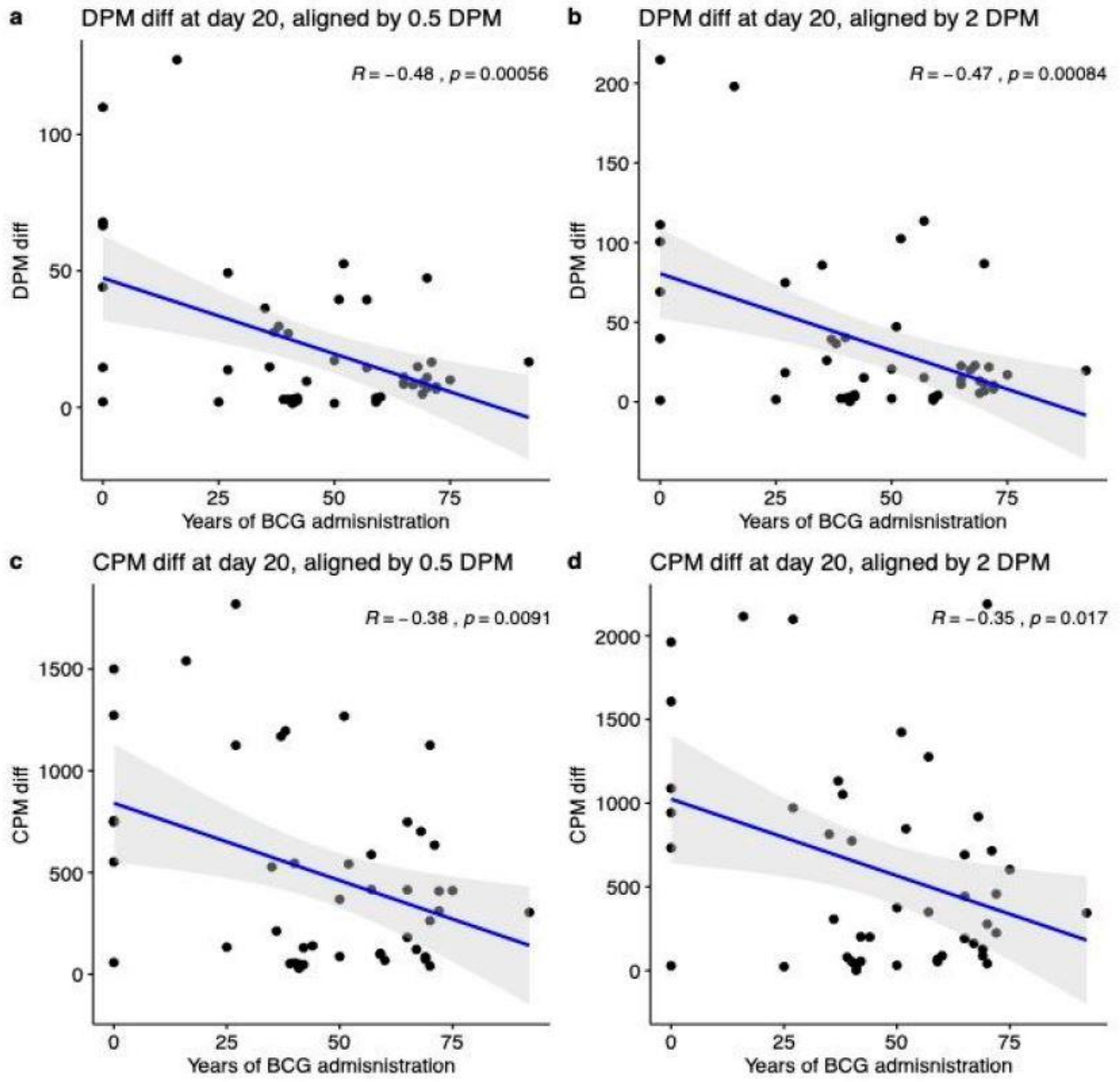

Figure 10: Statistical analysis of COVID-19 outcomes and years of BCG administration. All correlations were measured at 20 days following the alignment key date. Correlations of years of BCG administration with DPM = 0.5 (a) and DPM = 2 (b). Correlation with cases per million (CPM) diff. at 20 days when the key date was defined as CPM = 0.5 (c) and CPM = 2 (d). DPM diff. and CPM diff. are calculated by the differences in the numbers from the measured date to alignment date. Shaded areas represent the 95% confidence intervals (modified from Klinger et al., 2020).

4.3 Other candidates in trial

Several other candidates are also showing promising results and already in trial stage. India is one of the pioneer countries who are developing several candidates in various sector. For example,

- Zydus Cadila, an Indian pharmaceutical company, is developing a vaccine named as ZyCov-D. It is developed using a non-replicating plasmid containing the novel coronavirus gene on a DNA platform, making it safe than other candidates (Kumar et al., 2021). The Phase III trial is expected to launch by the company to test the vaccine effectiveness on around 30,000 people in march (The Economic Times, 2021).
- Another vaccine is being developed by Hyderabad-based Biological E Ltd, the first Indian private vaccine-making company, in collaboration with US-based Dynavax and Baylor College of Medicine. The company plans to recruit 20,000 to 25,000 participants for late-stage trials across India (REUTERS, 2021)
- India's first mRNA vaccine, named as HGCO19 is being developed by Pune-based Genova Biopharmaceuticals in collaboration with Seattle-based HDT Biotech Corporation. This mRNA vaccine transports the molecular instructions to make the protein in the body through a synthetic RNA of the virus causing the immune system to response against SARS-CoV-2 (Gennova Biopharmaceuticals Limited, 2021).
- An intranasal vaccine known as BBV154 is being developed by Bharat Biotech. It is a novel adenovirus vectored vaccine which will be a single-dose regimen (Bharat Biotech, 2021).

Chapter 5

Pre and post development challenges

5.1 Genetic diversity

One hypothesis is that SARS-CoV-2's extraordinary fast transmission may be driven by viral mutations due to its evolution. A systematic evaluation using whole-genome sequencing discovered 93 mutations containing 42 missense mutations across all SARS-CoV-2 genomes. Among the viral proteins all the major non-structural and structural proteins display abnormal mutations and most variations occur towards the ORF1ab polyprotein (29 abnormal mutations) and glycoprotein (eight abnormal mutations) in the spike surface. A more in-depth study of SARS-CoV-2's intraviral and virus-host protein–protein interactions revealed several findings:

(a) the spatial distributions of mutations affecting protein functional surfaces are found in a large number of SARS-CoV-2 proteins and were also examined in terms of human SARS-CoV-2's ligand binding capabilities, and

(b) All protein-binding sites of non-structural proteins showed fully conserved residues supporting the notion that mutation groups are unlikely to disrupt viral protein-protein interaction. Taking advantage of all the information currently available, it is assumed that the low variability within the new pandemic virus contributes to the development of a practical vaccine to protect against the new strain of the virus (Ghaebi et al., 2020). In December, an incredibly quickly spreading variant of SARS-CoV-2, known as B.1.1.7, was first reported in the United Kingdom which caused fear among the mass people. Scientists assuming that it can be more deadly than earlier versions (The Wall Street Journal, 2021).

5.2 Immunological challenges

The recognized immunodominant antigens and the protective immunity mechanisms displayed in animal models such as mice, guinea pigs and rabbits, can vary significantly from humans. The mouse is a quite popular model used in the production of vaccines, but its immune system is well known to differ very fundamentally from that of humans. Their classes and subclasses of antibodies do not correlate correctly in terms of activity and abundance in terms of adaptive immunity; for example, high concentrations of IgA1 and IgA2 are present in human serum while murine IgA is of one class and present at very low levels in serum (Saif, 2020). There is also evidence that suggests the polarization of T-helper (Th) cell subsets is not as straight cut in humans as it is in mice, and that Th differentiation regulation might be different as well. In addition to the physiological variations between animals and humans, the well-controlled laboratory conditions under which animal studies are conducted pose a potential cause for variation when advancing the research to human trials. Bad results have been documented in several Phase II clinical trials (Oyston & Robinson, 2012), possibly due to a normal tendency of impaired immune response between vaccine receivers or targeted population. In these challenging conditions, vaccine formulations have to be found which can thrive. In light of this, there is a need for increased production and use of experimental infections with human challenges (Oyston & Robinson, 2012).

5.3 Safety Concerns

Safety is the most critical concern that should be addressed during the production of drugs and vaccines and some scientists recommend that we should not hurry to deploy COVID-19 vaccines and drugs without appropriate safety assurances (ISERSON, 2020). For example, while S protein is a promising candidate antigen for the production of vaccines, it also displays other biological activity in addition to receptor binding and membrane fusion. Previous research has shown that

full-length spike protein may leads to severe liver damage which can cause increased infection. This has been identified as an antibody-dependent enhancement (ADE), and this effect will likely be triggered by spike protein-specific antibodies. To solve this issue, further basic research on the structure and function of this protein should be carried out, and the introduction of mutants of key residues in antigen design should be done (Zhang et al., 2020). To increase safety, it is proposed that vaccine virus should be cultivated on cells of a species that is different from the species which is the target of the vaccine. Nevertheless, changing a self-species cell substrate is not always the right solution and it is seen that many infectious agents have been shown to jump the species barrier. In twentieth century, more than 30 emerging infections were recognized, the majority of which were of zoonotic origin. Wildlife constitutes an important reservoir of new pathogenic agents for humans and domestic animals (Pastoret, 2010). Recently, data around United Kingdom as well globally indicate that groups of Black, Asian and Minority Ethnic (known as BAME) are at elevated risk of COVID-19 infection and death. Throughout extensive data analysis from several sources across UK, researchers found out that death among the BAME groups due to COVID-19 is significantly higher than other groups such as White people (Aldridge et al., 2020). It was also observed that COVID-19 mortality has been reported to be reasonably high in patients 65 years of age or older. In the largest series recorded from Italy, the mortality rate in patients 65 years of age or older was 36% compared to 15% in younger patients (Yanez et al., 2020).

5.4 Time frames

Human-use vaccines are manufactured in facilities that conform with current Good Manufacturing Practice (cGMP) to ensure that vaccines are of constant quality and protection. This needs dedicated equipment, skilled staff, adequate documentation, and cGMP quality raw material and most importantly a long time (Figure 11). These processes need to be planned or updated to suit

the vaccines with SARS-CoV-2. For some vaccine candidates in the preclinical phase, such methods do not yet exist and have to be established from start (Organisation for Economic Co-operation and Development, 2020). In order to assess the safety of vaccine candidates in humans, clinical production of vaccines typically starts with minimal phase I trials. These are accompanied by phase II trials, and ultimately phase III trials. Nevertheless, this scheme could be compressed in an unusual situation like the current one, and an expedited regulatory approval process could be created. It takes time to deliver and administer the vaccines. It will likely take weeks to months to vaccinate a large portion of the population. It is extremely likely that they will require more than one dose of the vaccine as seen in case of the potential vaccine candidates. In such cases, prime-boost vaccine regimens are commonly used, and the two vaccines are normally spaced 3–4 weeks apart. After the second vaccine, protective immunity is expected to develop in just 1–2 weeks. But this extends to the timetable for another 1–2 months. Even if alternatives to any of the above-mentioned steps can be found, it is uncertain that a vaccine will be available within six months of the start of clinical trials. Rationally, SARS-CoV-2 vaccines are not available for a further 12-18 months (Amanat & Krammer, 2020).

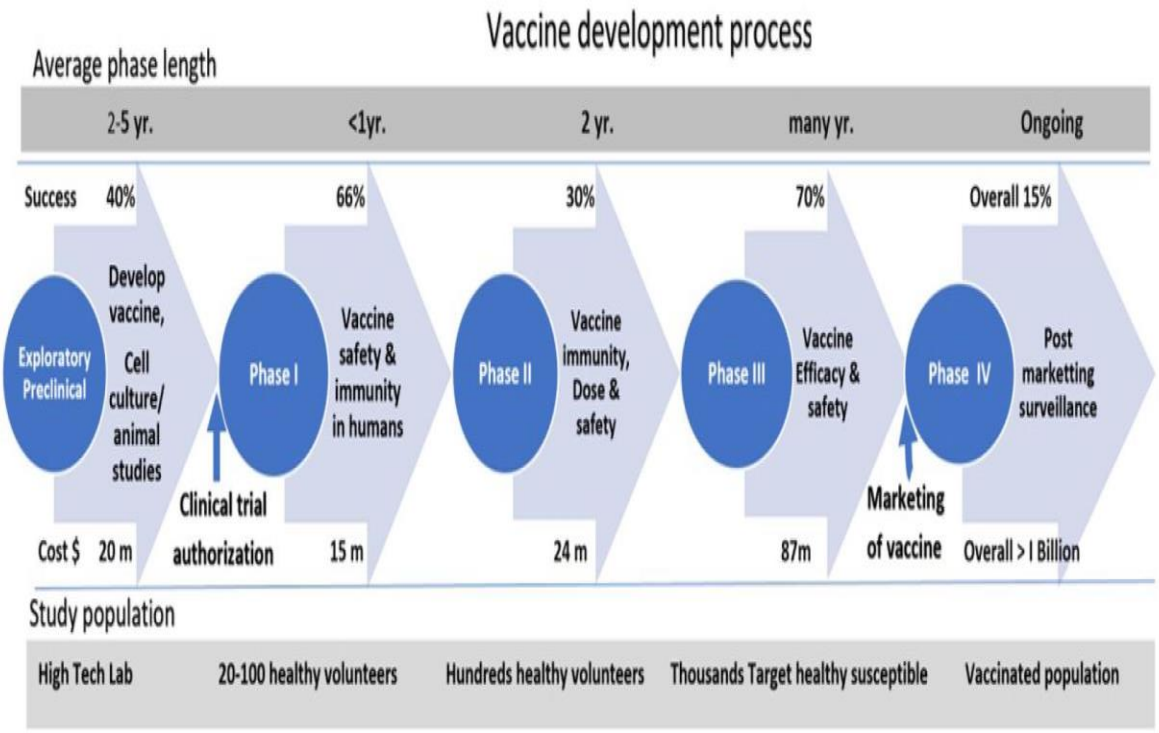

Figure 11: Schematic drawing showing steps in vaccine development. The vaccine development follows a unique stepwise pattern and is broadly divided into Exploratory, Preclinical, Clinical, and Post-marketing stages. The clinical-stage is divided into 3 phases, namely phases I, II, and III. There are 2 regulatory permissions needed namely 'Clinical Trial Authorization' before the clinical stage to allow 'First-in-human' testing and marketing of the vaccine after successful clinical trials (modified from Khuroo et al., 2020).

5.5 Preclinical evaluation

In spite of the rapid advancement in phase I/II clinical trials of many vaccine candidates, comparatively few reported preclinical data are available for critical study. Therefore, it is not clear to what extent these animal models predict the immunogenicity, efficacy and safety of the candidate vaccine in humans (Saif, 2020). In this respect, it remains to be seen whether a SARS-CoV-2 vaccine can be successfully produced before strong clinical evidence of theory is obtained, and hopefully such evidence would come from a efficacy study with placebo-controlled trials. To speed up the production of COVID-19 vaccines, novel approaches have been suggested and implemented for the strategy of clinical trials and enhanced versatile regulatory approval

pathways. As such, many candidates for the vaccine have already reached clinical trials without the full available data on preclinical effectiveness. For certain groups, some may need emergency use of the vaccine, such as health care staff, even before clinical trials are complete. Regulated human challenge trials were suggested for candidates for the SARS-CoV-2 vaccine to replace the traditional phase III clinical trial to boost up research and eventual implementation of successful vaccines. Such an approach could save the licensing process for several months. But others were challenging this strategy or other regulatory workaround or speed up (W. Chen, 2020).

5.6 Price, profits and market analysis

With a lot of underlying vaccine research being carried out in laboratories or non-profit organizations, it must be recalled that vaccines are formulated and sold by pharmaceutical companies. Thus, when contemplating the production of vaccines, one should not ignore the business. For pharmaceutical companies, one problem is that demand doesn't seem to fit with payment capability. Therefore, high pricing has been proposed for vaccines which are already formulated for high-income countries as a way to help both parties (Ella & Mohan, 2020). The approach, however, triggers understandable anxiety in developing nations. In this stage, pharmaceutical companies could also be concerned that by supplying affordable vaccines, inexpensive vaccines available in developing nations may possibly pose a threat to their profitable rich nation markets. Often a new vaccine is developed by just one manufacturer and, thus, market rivalry is not a catalyst for minimizing costs. This can restrict access to effective vaccines, especially in developing countries where cost-benefit analysis may be the primary influence compared to poorer countries where the deciding factor is accessibility. Real costs for the manufacture of new vaccines are not disclosed by pharmaceutical companies. For a single vaccine, popular R&D estimates concentrate mainly on the cost of developing new drugs and fall within a

range of 1-2 billion dollars. The high failures are one reason which is often given for these massive costs. The cost of research , development and clinical trials is especially high, and the organization needs to recover its spending that could have locked up money for a decade or more (Oyston & Robinson, 2012).

5.7 Ethical issues

Human challenge trials (HCTs) provide an opportunity to accelerate the production of vaccines for SARS-CoV-2. In HCTs, a candidate vaccine is given to volunteers, followed by an infectious pathogen dose (Nguyen et al., 2020a). The effects of this infection are monitored, offering a rare opportunity to determine the efficacy of a candidate vaccine. Historically, HCTs provided valuable information regarding interactions between human and pathogenic agents. But it is unclear if clinical endpoints applicable to the field are ethically permissible for research in HCTs. From the participant risk perspective, it is optimal to choose the minimum infectious dose of challenge virus needed to induce mild disease in most participants, likely using an attenuated strain of virus to achieve this result (Palarach et al., 2017). Even so, it is likely that vaccine candidates would more easily abrogate serious disease than moderate disease. HCTs may also present potentially less severe risks. HCTs could expose trial staff to the virus unwittingly, or accidentally release virus into the surrounding environment, all of which could lead to wider outbreaks. HCT teams should meet with the local community and other relevant stakeholders well in advance and take all appropriate steps to mitigate those risks (Nguyen et al., 2020b)**.**

5.8 Regulatory aspects

Developing vaccines typically takes at least 10–15 years, from preclinical research to licensing (Figure 11). Other than FDA (Federal Drug Administration), there are many other regulatory bodies regionally, e.g., EMA (European Medicines Agency) or country-wise, e.g., Brazilian Health

Surveillance Agency, commonly known as ANVISA, that are involved in approving the vaccine in their territories. Therefore, regulatory aspects pose a challenge in the development of the vaccine. On account of the urgent need for SARS-CoV-2 vaccines, however, the timeline for their production and approval would need to be considerably reduced, preferably to months rather than years. It has been possible only because of the cooperation and coordination among the stakeholders, e.g., funders, vaccine developers, regulatory authorities, policy makers, governments etc., though it put a considerable strain on regulatory agencies to perform all the normal work in a considerably shortened time frame. As the final product is a vaccine, it is much more important to maintain a well-controlled and highly reliable manufacturing process, with rigorous monitoring and data collection. Quality of design, quality assurance, and quality control monitoring for product release is more complicated given that vaccine development requires a biological process. Development, validation and optimization of the manufacturing process, and the use of the most efficient host cell line available, while reducing sources of variability would help ensure quality of the product batch to batch (Abu-Raya et al., 2020).

5.9 Vaccine distribution

To defeat this pandemic, not only the development of a successful vaccine but also its proper distribution among all classes of people around the world is also a hugely challenging task. This modern vaccine business can lead to serious trouble if it isn't handled properly. Pfizer & Moderna vaccine require several storage requirements including very cold temperature (Vox, 2021). Many developing countries like Bangladesh don't even have these storage facilities. Therefore, maintenance of the vaccine won't be easy. Another important factor is about the supply and demand of vaccine. In this midst of crisis, everyone needs vaccine as soon as possible but vaccinating everybody within a short period of time is a tough task. Moreover, some countries

don’t have enough manpower and administrative capability for conducting vaccination program smoothly. As a result, it is speculated that even though vaccine will be available after a certain period of time, distributing them will need much efforts and skills.

Chapter 6

Conclusion and future Aspects

6.1 Conclusion

The planet has been facing one of the worst global health crisis and economic catastrophe ever, and one of the decisive solutions is to provide an effective and secure vaccine in the shortest possible timeframe to as many people as possible. A few vaccine candidates after their successful clinical trials have been being in the distribution but this is not enough. We urgently need to develop more vaccine candidates against SARS-CoV-2 infection. A number of pharmaceutical companies and research institutes around the world have been continuing their COVID-19 vaccine research endeavors. In this journey, there have been difficulties in both research and development as well as policies aimed at setting precautionary, preparatory steps in the development and use of a SARS-CoV-2 vaccine. Looking back, there are many examples of pandemics such as the Spanish influenza pandemic of 1918, the most serious pandemic in history that happened in three waves over two years that affected about one-third of the world's population and killed about millions of people. Although vaccine development appears to be attractive and urgent, it has been expected to face several challenges. The development of vaccine technology, recent promises of support, regulatory facilitations, and the pace shown have raised hope. Better understanding of the pathophysiology, immunopathology, and effective animal model facilitate the development of vaccines and some vaccine candidates have already been in effect. However, the recent findings and transmission of the new variants from the UK and South Africa have established a new fear (BBC News, 2021). Researchers are predicting the efficiency of the existing vaccines against the new variants though not by as much as it could for the normal existed strain. It is to be seen whether

the virus undergoes more and genetic transformation in future that can pose a huge threat to the developed vaccines. Even though there is still a gap in terms of information about the virus, scientists have been trying day and night to unfold the mystery about the virus and the vaccines as much as they can. So far, the vaccines seem to convey a positive hope with a very little unwanted incidents against the vaccination, but more and more effective vaccine candidates, their multifold production rate and smooth distribution worldwide should be accomplished to get rid of this pandemic. Finally, it must be said that this vaccine development endeavor has created history in terms of time frame, cooperation and coordination worldwide.

6.2 Future aspects

6.2.1 CTL peptide vaccine

While vaccine development has focused almost entirely on expressing a humoral immune response in the host by inoculation with whole protein antigen, an important alternative approach may be provided by CTL peptide vaccines that produce a T-cell response. Most preventive vaccines are intended to induce a humoral immune response, usually from a pathogen through the administration of whole protein. Usually, antibody vaccines don't offer a robust T-cell response. A T-cell vaccine is intended to induce a cellular immune response that guides CD8+ cells to extend and attack cells with the HLA Class I restricted pathogen-derived peptide antigen. Difficulties in achieving a stable immune response from peptide antigens and the restricted HLA existence of the CTL vaccines have limited their effectiveness in protecting individuals from infectious disease. The adjuvant microsphere peptide vaccine platform integrates unmodified peptides which make rapid production and deployment possible to respond to a new viral threat (Herst et al., 2020).

6.2.2 B-cell engineering

While several factors can be attributed to the verity of vaccine production, an approach based on genome editing to replace the endogenously encoded antibodies with antibodies targeted at specific antigens in human B-cells may prove to be an effective strategy for developing a secure, efficient, and long-lasting vaccine. In theory, genome editing methods controlled by CRISPR/Cas9 have the ability to edit mammalian cell genomes with unprecedented precision and this method is not restricted to correcting the faulty sections of the genome. Genomes may be modified and repurposed directly for important objectives of enhanced and optimized functions. With this assumption, it can be speculated that engineering human B-cells will be possible for a similar method. To this end, well-organized expression of unique antibodies can be achieved in these cells under the guidance of endogenous regulatory elements accountable for the development of antibodies. Vaccines cause B-cells to develop antibodies to particular pathogenic antigens (epitopes) (e.g., S-spike protein in SARS-CoV-2). B-cells accomplish this fate by rearrangement of the three key elements of the antibodies in their genomes. Some causes for vaccine failure are that such a rearrangement of the gene does not take place quickly, may be delayed or may not last long. This is an additional explanation why B-cells are engineered in such a way that they continue to generate the necessary antibodies continuously as and when needed (Faiq, 2020).

6.2.3 Novel multi epitope-based vaccine

For deep antigen analysis, immuno-informatics can be applied to a full protein data set of the virus and can thus save time and expense in developing a COVID-19 vaccine. This would promote the early production of a vaccine and the formulation proposed can be subjected to experimental trials immediately (Ahmad et al., 2020). By applying suitable approaches, prediction about how an epitope-based peptide vaccine can be developed can be achieved. At first, obtaining data regarding

COVID-19 infected patient cases from various authentic sources such as NCBI need to be done. These data can provide information for understanding the genome sequence of SARS-CoV-2. After that the Artemis Comparison Tool (ACT) software can be used comparing complete genome sequences (Carver et al., 2005). In the next step, the Molecular Evolutionary Genetics Analysis (MEGA) software will be used for the comparative analysis of molecular sequences. As shown in the workflow of the epitope-based peptide vaccine in figure 12, several other software needs to be used for various purposes like BioEdit for analyzing the envelop (E) proteins of coronavirus, Immune Epitope Database (IEDB) tools for T-cell epitope analysis, RaptorX for creating structural visualization of E protein, autodock for molecular docking and UCSF Chimera for obtaining final results. The Major histocompatibility complex (MHC) class I and II epitope prediction were estimated before the E protein analysis.

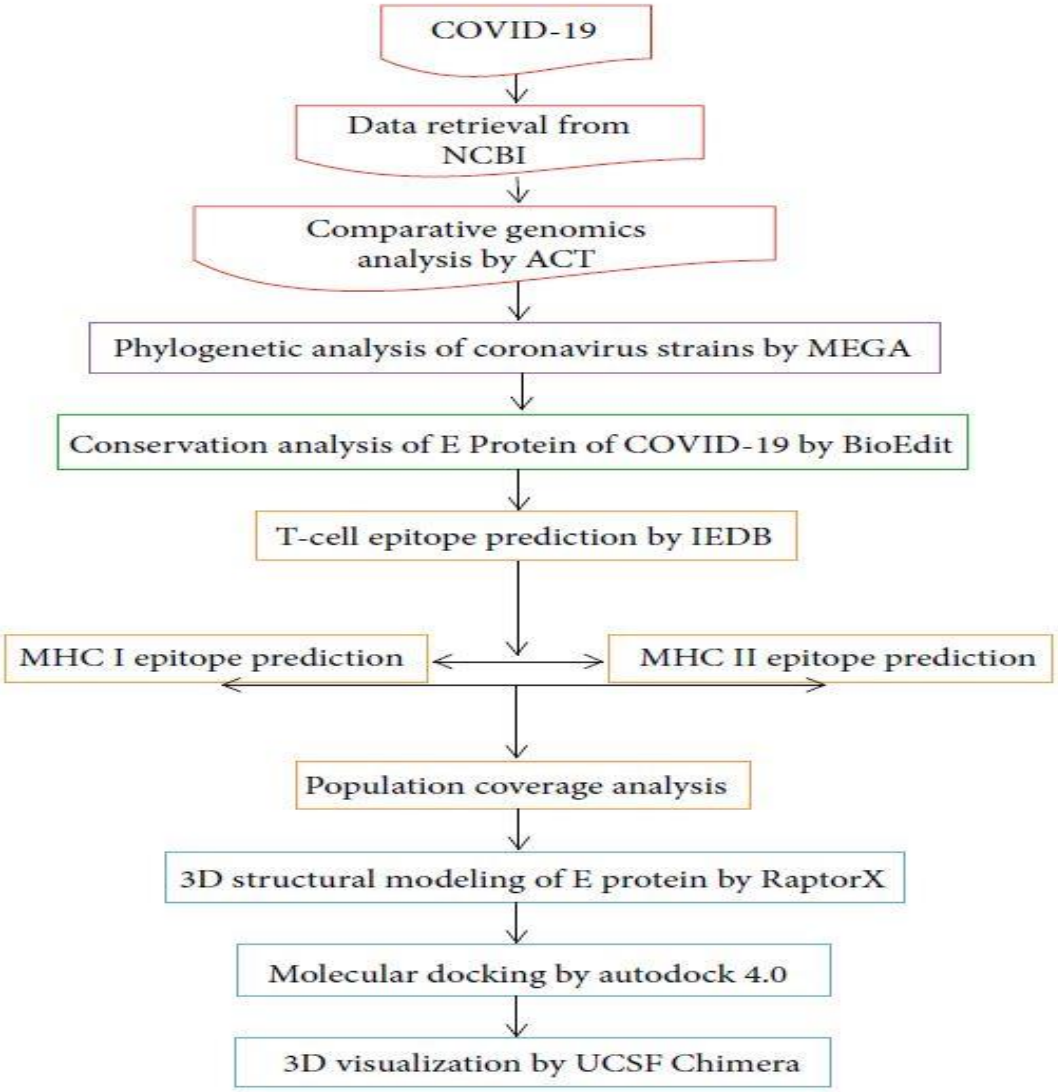

Figure 12: Descriptive workflow for the epitope-based peptide vaccine (copied from Abdelmageed et al., 2020)

Peptide-based vaccines do not require an in vitro culture to make them biologically safe, and their selectivity enables accurate immune response activation. The central mechanism of the peptide vaccines is based on the chemical method to synthesize the recognized immunodominant B-cell and T-cell epitopes that can trigger complex immune responses. To make it immunogenic, a B-cell epitope of a target molecule may be bound to a T-cell epitope. The T-cell epitopes are small fragments of peptides (8-20 amino acids) while the B-cell epitopes may be protein. Hence,

developing a peptide-based vaccine to predict corona envelope (E) protein epitopes using immunoinformatic analysis would be useful. It is suggested that rapid further studies are required to prove the effectiveness of the expected epitopes as a peptide vaccine against this emerging infection (Abdelmageed et al., 2020).

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