 doi:10.20944/preprints202208.0204.v1

Review

Vaccine Cocktail as a Future to Fight Against Family of SARS-Cov-19

Deepali Sharma[1], Nidhi Sharotri[2*], Suvardhan Kanchi[3,4], Surendra Thakur[5,6]

[1] Integrated Behavioral Health Research Institute, San Gabriel, CA 91775, United States
[2] Department of Chemistry, Sri Sai University, Palampur, Himachal Pradesh, India
[3] Department of Chemistry, Sambhram Institute of Technology, M.S. Palya, Jalahalli East, Bengaluru 560097, India
[4] Department of Chemistry, Sambhram University, Khamraqul Street, Jizzakh City 130100, Republic of Uzbekistan
[5] KZN e-Skills CoLab, Durban University of Technology, Durban, South Africa
[6] Department of Information Technology, Durban University of Technology, Durban, South Africa
* Correspondence: ksuvardhan@mail.com

Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 commonly known as SARS-CoV-2 is the utmost challenging pandemic that attracted scientific community to discover therapeutics as well as vaccination solutions to control SARS-CoV-2. Different diagnostic and detection methods have been improved and re-introduced from the previous observations of SERS and MERS. Due to the high mortality rate and fast spread, researchers all around the globe gathered to develop an effective vaccine. The review article summarizes various types of vaccines, mutants of virus, strategies in tackling virus, vaccine development and its global distribution with the focus on the use of mix and match of vaccines to fight the virus. The reported studies depict the design and production of successful COVID-19 vaccines with good efficacy as the selected vaccine population embrace high-risk personages i.e. above the age of 60, frontline workers and other essential service workers. We have targeted at delivering an outline of the determinations devoted to an effectual vaccine for novel Covid-19 that has restricted the domain by means of human health, economy, as well as life.

Keywords: Vaccine cocktail; COVID-19; MERS; SARS; Viruses

1. Introduction

In the current article, we have reviewed the present state of knowledge on the mutants of COVID-19, different strategies employed for the vaccine development and their global distribution. In addition, we have primarily focused on the chemistry involved in the vaccine development and the future of 'cocktail' of vaccines to fight the transmission of COVID-19 in the population. Extensive research is being carried out and updated in the publications, which are growing in numbers. Although a lot of review is available based on the acquired knowledge and evidence, we want to draw the attention of the readers to the combination or 'cocktail' of vaccines that could prove to be effective in combating the COVID-19 virus.

The emergence of coronavirus disease in the beginning of the year 2019 (COVID-19) has affected millions of mortalities worldwide till date. The pandemic forced governments of the countries all over the world to take significant measures from increasing the personal protection, emphasizing on the social distancing, proper covering of face using surgical/non-surgical masks and prioritizing the vaccination drive to tackle and lower the infection rate[1]. The CDC known as the Centers for Disease Control and Prevention brought changes in its instructions on April 3, 2020 and advised the usage of masks in the public[2]. The evidence based on the asymptomatic and pre-symptomatic people who were infection carriers led to the policy change[3, 4]. One of the evidences is shown in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

Figure 1 which depicts the family cluster of infected persons based on positive qRT-PCR results without any indication or symptoms[4].

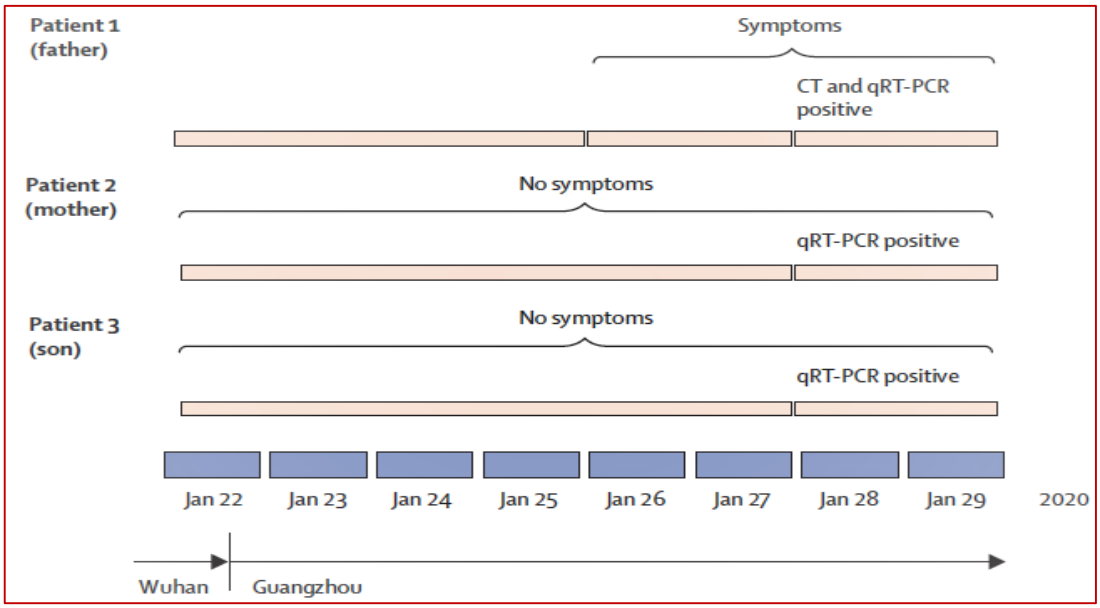


Figure 1. Chronology of symptom onset and identification of positive SARS-CoV-2 findings on qRT-PCR and CT among the family cluster. qRT-PCR=quantitative RT-PCR. Adapted from ref. 4.

Figure 1 represents a family of 3 where a 35-year old male patient (number 1) had shown some clinical signs or symptoms, i.e. a reduced lymphocytic count, an abnormal image of CT chest and a positive qRT-PCR test; whereas 33-year old female patient (number 2) and another 3-year old teenager patient (number 3) did not have any symptoms (asymptomatic) but gave positive result with qRT-PCR.

Although effective measures have been taken including the lockdown of many services (non-essential), schools, travel to curb down the disease but still the number of COVID-19 cases increases on daily basis causing social and economic disruption. The scientific community is putting concentrated efforts in the development of vaccines and out of which many of have been tested, approved, rolled out in the market, and already being administered to people. These medications or vaccines are needed to get away with the COVID-19 pandemic and bring the world back to normalcy. The latest information through COVID-19 vaccine tracker and landscape (**Figure 2a** and **2b**) by World Health Organization (WHO) has been development been shown below as per June 8, 2021[5].

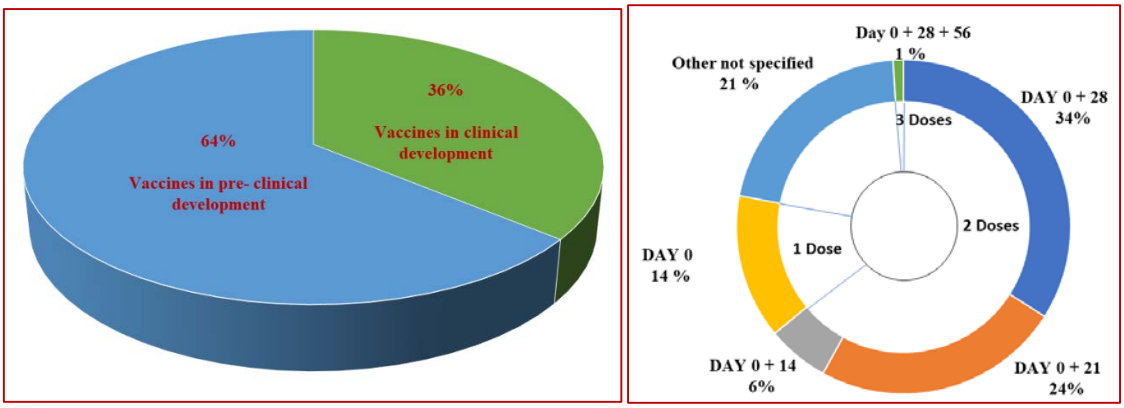


Figure 2. a. Vaccines products in clinical development**; Figure 2b.** Number of doses and schedule of vaccine in clinical phase.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

Most of the COVID-19 vaccines are based on the use of spike protein (S protein) of SARS-CoV-2 or a fragment of it as an immunogen that acts as an capable agent for inducing immunity responses[1] (**Figure 3**). The spike protein is comprised of S1 and S2 subunits; in which S1 subunit has a domain for receptor binding that finally recognizes and bind to the receptor angiotensin-converting enzyme 2 (ACE2) of host cell and the S2 subunit facilitates the pathological (viral) cell entry. The S protein which is present on the surface of the virus and is composed of trimeric class I TM glycoprotein is crucial for the infection. The spike proteins are important target for virus neutralization and also leading candidate for therapeutic antibody development[6, 7] (**Figures 4 and 5**). The strategies for the virus neutralization includes the use of variants of soluble human ACE2, antibodies from the SARS-CoV-2 convalescent patients, nanobodies and interacting them with the spike protein[8, 9].

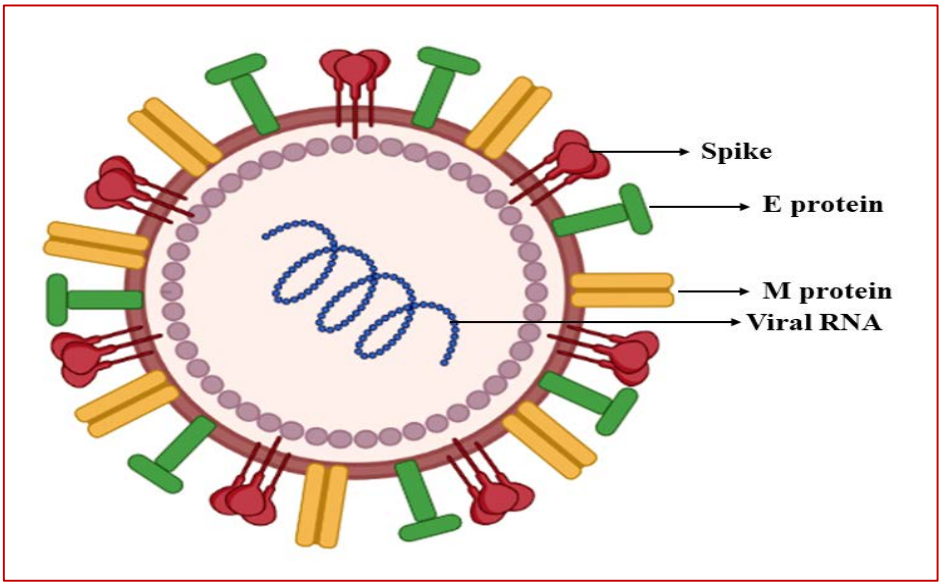


Figure 3. Structure of SARS-CoV-2 with spike protein.

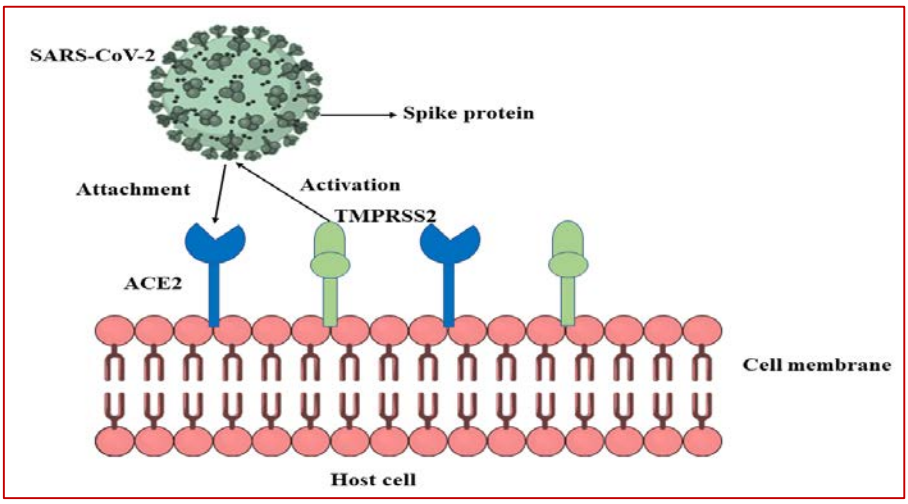


Figure 4. The spike protein of SARS-CoV-2 is activated by protease TMPRSS2 before it binds to ACE2 receptor.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

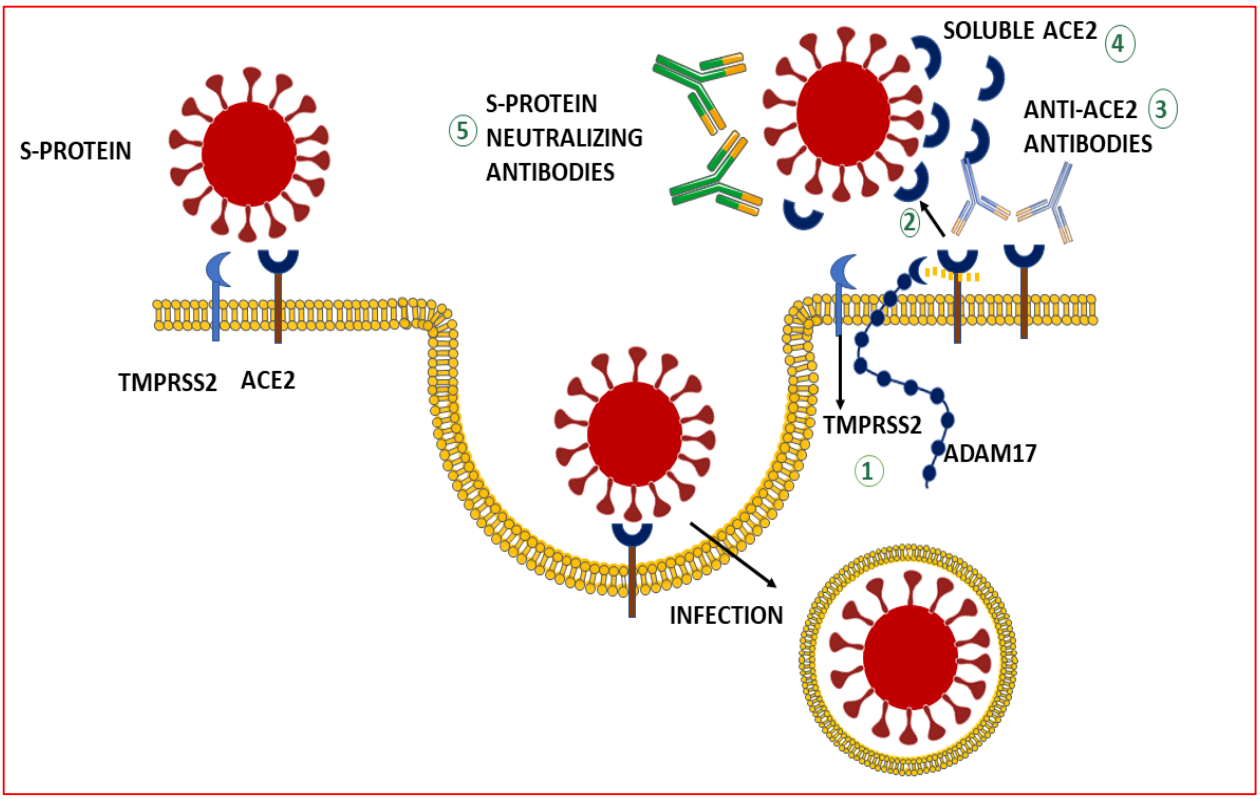


Figure 5. Coronaviruses engage with host-cell surface receptor and deposit their RNA genome into the host cytoplasm through endocytosis or direct membrane fusion through MPRSS2 & ADAM17 that cause ACE2 shedding; S-protein of SARS-CoV-2 binds with ACE2.

1.1. Family of Viruses (types and structures)

Viral infections occur when submicroscopic infectious agents known as viruses subjugates an organism body completely[10-15]. Once it enters the organism body, the virus produces new extracellular infectious form of virus outside the host cell that contains RNA or DNA along with capsid (protein coating) called Virion. This extracellular infectious form of virus is mainly the cause of disease. A number of viruses (tiny organisms) causing various infection diseases exist almost everywhere **(Table 1).**

According to Protocol, an epidemiological control on most of the viral infections possibly depends on the number of steps, which includes[16];

a) Segregation/ Isolation of cases
b) Quarantine or Sequestration of diseased person
c) Protection by adopting infection control measures
d) Mass vaccination

The above steps are responsible to control various viral infections due to inadequacy in availability of particular antiviral treatment for most viral infections. Commonly known acute viral infections are based on exanthematous, diarrheal, neurological, or even respiratory. These infections can overlie with one another and emerge as **seasonal epidemics** (in the last few durations) and attacks mostly on young population having non-immune hosts[17].

Arthropod-borne viral diseases called Arboviral syndromes occurs in warm drizzling seasons which are connected with the occurrence of various neurological diseases or infections known as hemorrhagic fever (dengue), Japanese encephalitis or West Nile virus[18]. Several immedicable blood-borne viral diseases like human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV), are spreading in certain geographic regions because of perinatal or vertical transmission or specific human behaviors. A number of atrocious viral contagion like HIV, HCV, polyomaviridae virus, HBV, and papillomaviridae (PV's) virus are also associated with the emergence of cancers. Around 70% of evolving viral illnesses like Ebola virus, SARS-CoV **(**severe acute respiratory syndrome coronavirus), and MERS-CoV

 doi:10.20944/preprints202208.0204.v1

(Middle East respiratory syndrome coronavirus) are connected with severe or acute epidemics after the transmission of infection from bats (Chiroptera) or other creatures to mankind[19].

 doi:10.20944/preprints202208.0204.v1

Table 1. A number of viruses causing various infectious diseases

Chief viral families	Types of viruses within the same family	Transmission mode	Main clinical disorders	Diagnosis measures	Treatment (antiviral)	Prevention (vaccine)	References
Herpesviridae	HSV-1, HSV-2	Contact and droplet	Oral or Genital herpes,	Serology, PCR and Viral culture	Valacyclovir, Acyclovir		[20, 21]
	VZV	Air-borne	Chickenpox,		Acyclovir, Valacyclovir,	Varicella for VZV infection	[22-24]
	EBV	Air-borne	Infectious mononucleosis				[25, 26]
	CMV	Air-borne	Roseola infantum		Gancyclovir, Cidofovir		[27, 28]
	HHV-6, HHV-7	Air-borne	Kaposi's sarcoma				[29, 30]
	HHV-8	Air-borne	Encephalitis		Gancyclovir, Cidofovir		[31, 32]
Orthomyxoviri-dae	Influenza A, B, C	Contact/ Droplets mode	Pneumonia, Pneumonitis, Upper respiratory tract infection, Pericarditis, Encephalitis	PCR, Viral culture, Immuno-fluorescent staining, Serology	Peramivir used for influenza A or B, Oseltamivir, Amantadine, Rimantadine, Zanamivir, and Favipiravir	Seasonal Influenza Vaccines like H5N1, H7N9, H1N1, H3N2	[33-36]
Filoviridae	Ebolavirus	Contact	Viral (hemorrhagic) fever	Serology, PCR, Viral culture	None	Ebola vaccine	[37-39]
Picornaviridae	Enterovirus, Hepatovirus, Poliovirus, Rhinovirus	Droplets	Respiratory illness; Hand, foot, and mouth disease; Hepatitis A infection, Aseptic meningitis, and Poliomyelitis,Myocarditis, Upper respiratory tract infection	Serology, PCR, Viral culture	None	Oral polio vaccine, Hepatitis A vaccine, Poliovirus, Poliomyelitis	[40-44]

Rhabdoviridae	Rabies virus	Contact	Rabies	Serology, PCR, Viral culture	Human rabies immunoglobulin	Rabies vaccine	[45-47]
Flaviviridae	Tick-borne encephalitis virus, Japanese encephalitis virus, Dengue virus, Yellow fever virus, St. Louis encephalitis virus, West Nile virus, and Hepatitis C virus	Blood- to-blood contact	Acute and chronic hepatitis, Hemorrhagic fever	Serology, PCR, Viral culture	Pegylated interferon/ Ribavirin/ Polymerase/ protease inhibitors	Yellow fever vaccine, Dengue vaccine (phase III)	[48-53], [54-57]
Paramyxoviridae	Mumps virus, Human para-influenza virus, Measles virus, Human metapneumovirus	Droplets	Measles, Upper respiratory tract infection, Mumps, Pneumonia	Serology, PCR, Viral culture	None	MMR vaccine for measles and mumps	[58-60]
Togaviridae	Equine encephalitis virus, Rubella virus, Chikungunya virus	Droplets	Chikungunya disease, Rubella	Serology, PCR, Viral culture	None	MMR vaccine for rubella disease	[61-63]
Retroviridae	HIV-2, HIV-1	Body fluid or blood to blood contact	Acquired immune deficiency syndrome	Serology, PCR, Viral culture	HAART	None	[64, 65]
Coronaviridae	Human coronavirus	Droplets/ Airborne	Pneumonia, Upper respiratory tract infection	Serology, PCR, Viral culture	-	-	[66, 67]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

In air-borne viral diseases, a virus enters through the airway and is possibly divided into categories: Upper airway and Lower airway infections.

An upper airway infection causes immunity deficient and immuno-competent criticality as one of the major clinical conditions. This includes viruses such as human rhinoviruses and echoviruses (common cold viruses) and influenza (mild) transmission due to their surface (epithelial) bounded action. The other types of viruses are those that produce rubella, herpes simplex virus [HSV], measles, mumps, and cytomegalovirus [CMV], etc. These viruses expand to rest parts of the body once the epithelium is invaded by them i.e., the outer layer of the body surface. In lower airway infections and pneumonia [68], an acute viral bodies cause serious respiratory syndrome in immune-competent adults and is termed as febrile respiratory illnesses (FRIs) shown in **Table 2.** The febrile respiratory illnesses viruses are arranged into two major classes such as myxoviruses (i.e. influenza A, B and C) and adenoviruses.

An Orthomyxoviridae virus (seasonal flu virus or Influenza) is an RNA virus, which has three subtypes i.e. A, B, and C that causes epidemics and pandemics due to their genetic variability property[69, 70]. The structure of influenza virion is approximately spherical and enveloped shape **(Figure 6).** The outer layer is a lipid membrane layer consisting of proteins (glycoproteins) linked to sugars called HA (hemagglutinin) and NA (neuraminidase). The protein part is responsible for determining the subtypes of influenza virus. The main symptoms disease causes are chills, fever, anxiety or malaise, headache, non-productive cough continues only for 3 or 4 days and even muscle pain. The main source of transmission is coughing or sneezing i.e. an airborne direction during main symptomatic period. The diagnostic techniques generally used are viral-cultures or PCR i.e. polymerase chain reaction amplification, nucleic acid tests and antigen determination tests. The medication treatments involve various neuraminidase inhibitors such as oseltamivir and zanamivir due to their significant resistance property[71, 72].

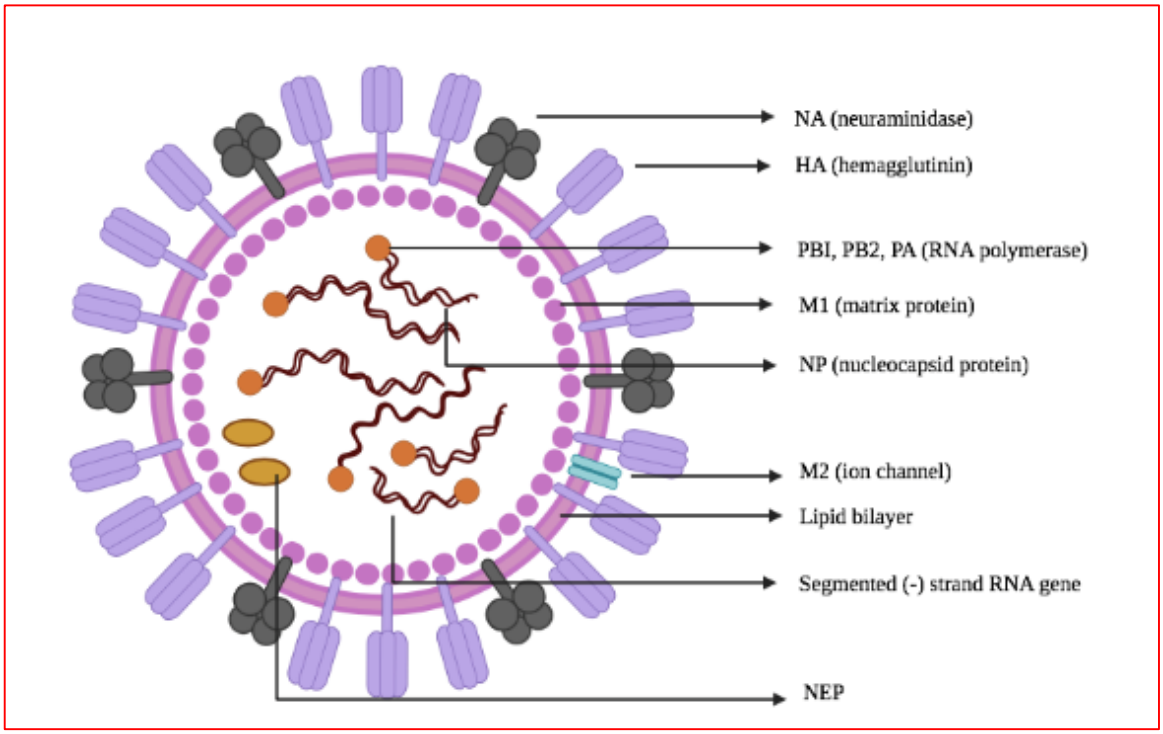


Figure 6. Structure of Influenza Virus.

Parainfluenza virus also called respiratory syncytial virus (RSV) have structural resemblance to influenza virus (RNA viruses), belongs to the family of Paramyxoviridae and also share various attributes with respect to epidemiology, clinical indications, and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

pathogenesis[73]. The RSV genome or Para influenza encodes 10 proteins out of which 2 are non-structural proteins. It possesses large envelope composed of glycoproteins, that contains fusion protein (F) and a second glycoprotein. In the parainfluenza viruses, the second glycoprotein is called hemagglutinin neuraminidase and in RSV it is known as G[74, 75] as shown in **Figure 7**. Transmission of disease takes place from infected secretions or fomites. It causes serious condition, especially in aged patients or persons having some severe respiratory diseases like chronic obstructive pulmonary disease [COPD], cystic fibrosis, and lung transplants. The clinical manifestations of Para influenza are found analogous to influenza virus. Various supportive tests used for diagnosis measures are clinical manifestations, viral isolation, antigenic detection tests, and PCR test. The uptake of bronchodilators, corticosteroids, and nebulized ribavirin plays important role in treatment of RSV[76].

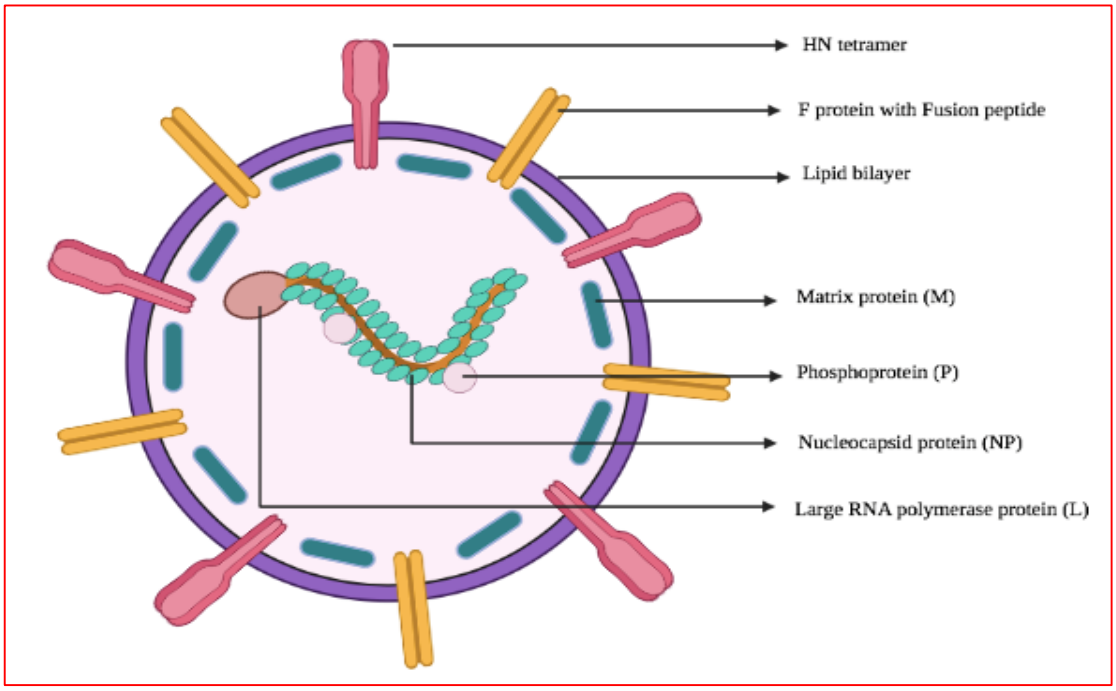


Figure 7. Structure of Para influenza Virus.

1.2. Different Viruses

1.2.1. Coronavirus-SARS (SARS-CoV-2)

Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-2) is a novel virus that resulted in first pandemic of the millennium[77, 78]. It belongs to the family of enveloped coronavirus i.e. coronaviridae family which contains encapsulated coronavirus single-stranded, positive-sense RNA viruses. SARS-CoV-2 has the same structural proteins as previously known coronaviruses. It contains envelope protein (E), spike glycoprotein (S), membrane protein (M) and nucleocapsid protein (N) shown in **Figure 3.** The N protein is known for coronavirus RNA synthesis. The major clinical symptoms are chills, fever, nausea, muscle pain and headache that further develop to respiratory alterations within 7-8 days and finally causes respiratory failure, severe hypoxemia and ARDS. The diagnosis measure includes PCR, viral cultures test, immunofluorescence tests and ELISA. In some cases, corticosteroids are prescribed for treatment from SARS-CoV-2. The possible transmission route is from airway, in form of droplets and even contact[79-81].

1.2.2. Adenoviruses

Adenoviruses (ADVs) are the most complex structured non-enveloped, icosahedral viruses. Its nucleocapsid contains 252 proteins in the form of 3 main types i.e., penton,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

fiber, and hexon based proteins shown in **Figure 8.** The hexon based proteins are the structural component that compose viral capsid. Whereas fiber and penton based proteins are responsible for entry of the adenovirus into host cells[82]. ADVs have been seen in mostly all vertebrates i.e., from fish to humans. They confirm dual character i.e., can behave as pathogens as well as therapeutic agent. ADVs have been known as basis of lower airway disease, rarely cases of pneumonia with ARDS i.e. Acute Respiratory Distress Syndrome. It may cause some extra-pulmonary symptoms such as hepatitis, gastritis, hemorrhagic cystitis, and meningitis. The mode of disease transmission is done via contact and droplets method. The diagnostic measures are conducted by using viral cultures and PCR test. Cidofovir and Ganciclovir are used for treating adenovirus[83].

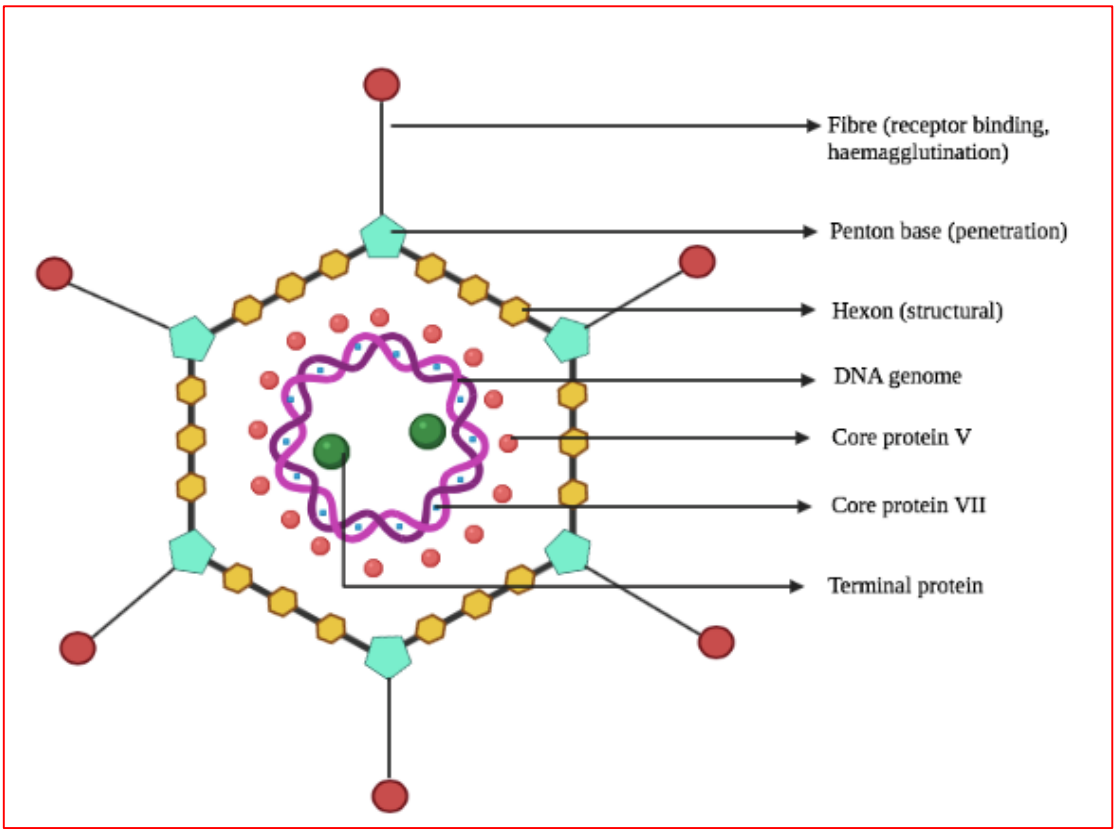


Figure 8. Structure of Adenovirus.

1.2.3. Hantavirus

Hantaviruses is also known as Orthohantaviruses, that becoming a threat for public health[84]. Hantavirus is negative single stranded (ss) RNA enveloped virus that is transmitted via small rodents. They duplicate in the host cell cytoplasm and are comprised of a four viral proteins, three single-stranded, negative-sensed RNA segments labeled as S (small), M (medium), and L (large) and spherical lipid envelope [85] and these are known as coding for the glycoproteins G1 and G2 (surface envelope), nucleo-capsid protein (NP), and RNA polymerase (RNA-dependent), respectively shown in **Figure 9.** The virus can be transmitted via contact with faeces or the urine of disease-ridden mice. Hantavirus produces two basic clinical disorders, which are hantavirus cardiopulmonary syndrome (HCPS) and hemorrhagic fever with renal failure syndrome (HFRS). The symptoms appeared are fever, muscle pain, chills, ARDS, coagulopathy, abdominal pain, respiratory failure, and shock. The diagnosis is constructed based on various serological tests. The treatment method comprises of administration of ribavirin in HFRS.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

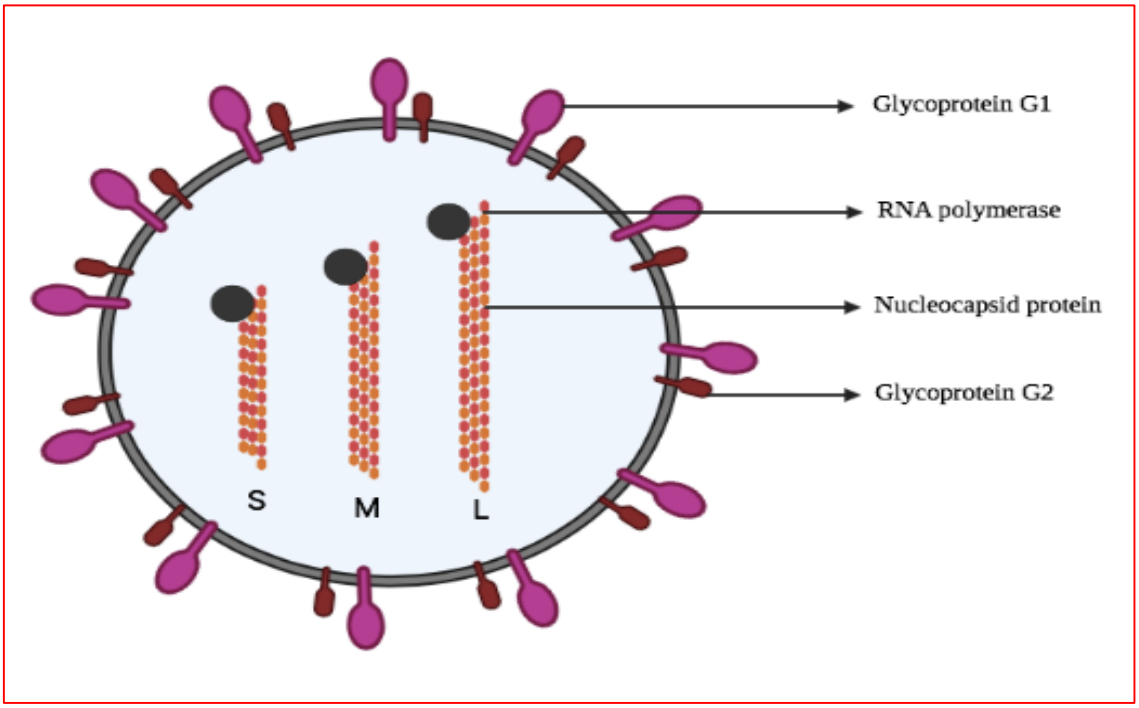


Figure 9. Structure of Hantavirus.

1.2.4. Ebola virus

Ebola virus belongs to *Filoviridae* family and the word *"filum"* means thread which means this filamentous virus has twisted thread shape. The virus is a negative-strand RNA virus having tubular or cylindrical shape that comprises of matrix[86, 87], viral envelope, and nucleocapsid components **(Figure 10).** Ebola virus disease (EVD) occurs because of virus infection, and it infects humans and primates, that finally causes fatal haemorrhagic fever. EVD are also known as Ebola haemorrhagic fever or iconic haemorrhagic fever, with most common symptoms such as malaise, fever, diarrhoea, headache, or vomiting. The infected person transmit virus via contact with body fluids (urine, saliva, blood, breast milk, faeces, semen, sweat or fomites). The treatment includes the use of monoclonal antibodies, convalescent plasma, anti-viral drugs like remdesivir[88, 89].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

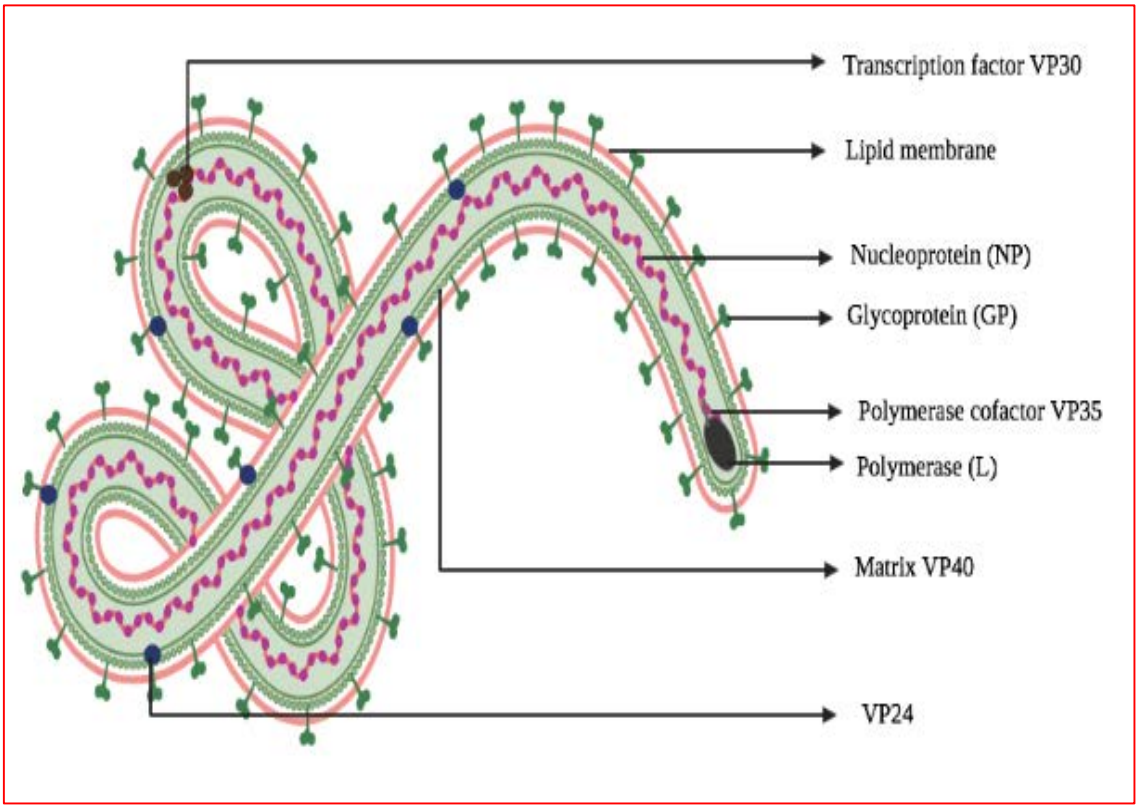


Figure 10. Structure of Ebola virus.

1.2.5. MERS virus

Middle East respiratory syndrome (MERS) is a caused by novel coronavirus disease, hence called Middle East respiratory syndrome coronavirus or MERS-CoV, a known viral respiratory disease[90]. The MERS-CoV genome consist of ORF1a and ORF1b which are two overlapping reading frames **(Figure 11).** The third genome encodes structural proteins, containing envelop (E), spike (S), nucleocapsid (N) and membrane (M) proteins. The major symptoms are shortness of breath, fever, cough, pneumonia, and diarrhoea also. Mostly patients infected with MERS-CoV infection are asymptomatic. MERS-CoV is known as zoonotic virus, that transmits between animals and human. It belongs to the family of *Coronaviridae* and has a large RNA viral genome[91].

 doi:10.20944/preprints202208.0204.v1

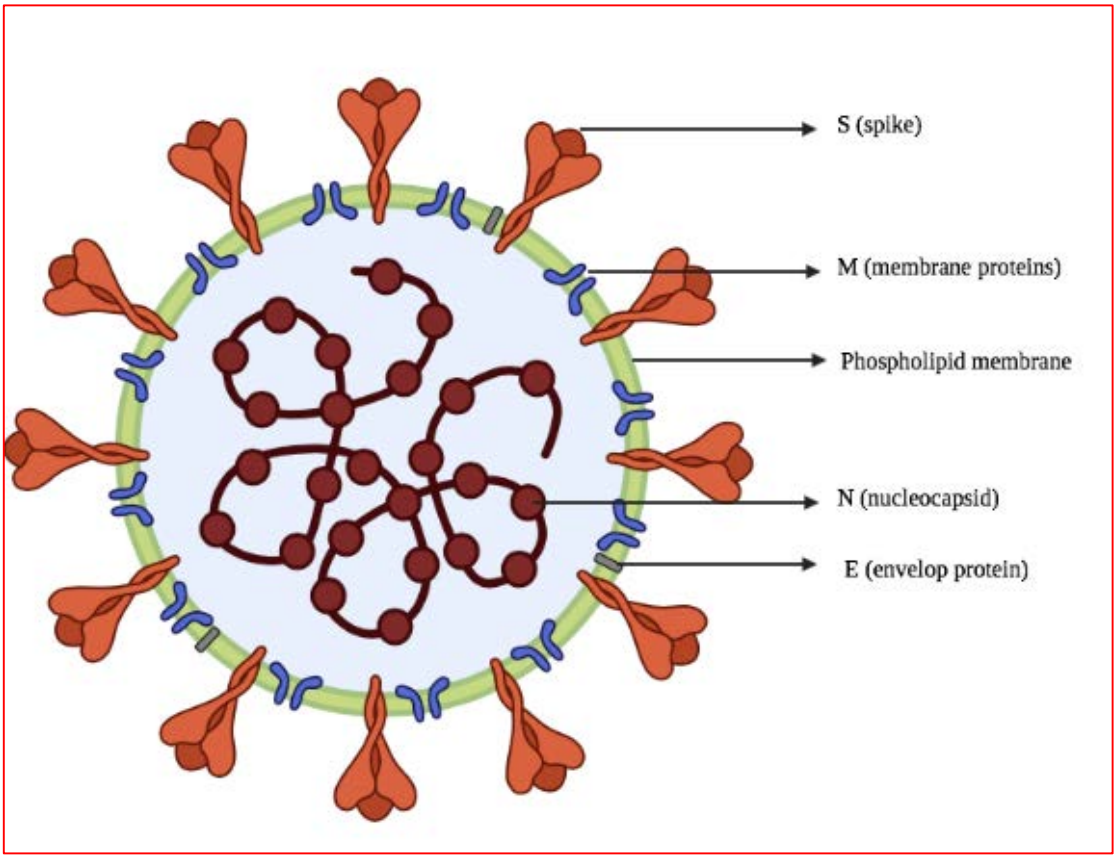


Figure 11. Structure of MERS virus.

3. Different mutants of COVID-19

In present pandemic situation, WORLD HEALTH ORGANIZATION and CDC has enlisted a number of variants or mutants of COVID-19 virus[92, 93]. A variety of genetic mutants or variants belongs to SARS-CoV-2 have been evolving and covering the globe during this pandemic condition. A SARS-CoV-2 Interagency Group (SIG) in The United States established a scheme, which categories COVID-19 virus into three main classes.

Table 2. Various types of febrile respiratory disorders

Name of the Virus	Epidemiology	Major symptoms	Diagnosis measures	Treatment method	Mode of Transmission	Mortality rate	Quarantine/ isolation	References
Influenza	Serious indications in risk groups	Pneumonia, Myocarditis, COPD and Encephalitis	Antigen detection test, PCR test and viral culture test	Neuraminidase inhibitors	Droplet as well as contact and sometimes aerial transmission	Less than 1%	Not required	69- 70
Respiratory Syncytical Virus/ Parainfluenza	Seasonal disease	Pneumonia, Bronchospasm and Bronchiolitis	Antigen detection test, PCR test and viral culture test	Nebulized ribavirin, bronchodilators and corticosteroids	Infected person secretions and fomites	Close to 10%	Contact isolation required	74- 75
SARS-CoV	Serious indications in risk groups and old age group	Hypoxemia, Respiratory failure and ARDS	PCR test , IF test, Cultures and ELISA Test	Corticosteroids	Aerial, Contact and droplet transmission	Near about 11%	Isolation required	77- 78
Adenovirus	Affect healthy population	ADRS, pneumonia and Extrapulmonary disease	Antigen detection test, PCR test and viral culture test	-	Transmission through contact and droplet	About 20%	Contact isolation required	82-83
Hantavirus	Contact with infected mice	Renal failure disorder, cardiopulmonary disorder and hemorrhagic fever	Serology test	Ribavirin	Contact with infected mice feces and urine	About 20%	Not required	84- 85
Ebola virus	Bush meat consuming human	Muscle pain, fever, vomiting, headache, chest pain, bleeding the the white part of eye	PCR test	Brincidofovi, Lamivudine, Favipiravir, Immucillin A, FGI (functional Genetics Inc.), Neplanocin A, Ebola vaccine rVSV-ZEBOV	Blood to blood, contact with infected body fluid	Above 20%	Isolation required	86-87
MERS-CoV	Serious indications in risk groups	Fever, dyspnea, cough, myalgia, Hyperleukocytosis,	PCR test, Serology test	Interferons (IFN), Ribavirin, Protease inhibitor, Chlorquine, Nitazoxzmide,	Transmit through infected person respiratory secretions	Above 20%	Isolation required	90- 91

 doi:10.20944/preprints202208.0204.v1

	Lymphocytopenia, CRP levels, and Hypoxemia	Alisporivir, Silvestrol, Corticosteroids

 doi:10.20944/preprints202208.0204.v1

3.1. Variant of interest

A variant or mutant with specialized genetic markers have been found under category of variant of interest. In this type of variant, mutation is associated with alteration in receptor binding site, minimized diagnostic and treatment effectiveness, almost diminished neutralization processing by antibodies that are generated in opposition with former infection or vaccination and finally increased disease severity or transmissibility.

Various characteristic traits of a variant or mutant of interest are,

a) Variation or mutation in particular genetic markers that affect diagnostics, transmission, and therapeutics of virus.
b) Mutation in current viral genome finally causes an abrupt increase in number of cases.

The various variants of interest which have been observed till now are enlisted below.

a) Eta-The Eta mutant or lineage B.1.525 was first identified by United Kingdom or Nigeria in December 2020. This variant is also named as VUI-21FEB-03 or VUI-202102/03 (Public Health England) and previously known as UK1188, 21Dor 20A/S:484K. It carries E484K-mutation same as found in the Zeta, Beta and Gamma, mutants[94]. The various characteristic features shown by Eta variant are reduction in neutralization process of monoclonal antibodies treatment and another possible reduction in neutralization due to post-vaccination.

b) Iota (lineage B.1.526)-Iota variant was initially detected in New York city of US in November 2020. Around 11 April, 2021, this mutant was found in at least 48 states of U.S. and in 18 countries. The main variation due to mutation of virus is reduced action of response for antibodies like combination of bamlanivimab and etesevimab that are previously used for monoclonal antibody treatment against virus[94].

c) Kappa or lineage B.1.617.1-The Kappa mutant is also known as lineage B.1.617.1, 21B or 21A/S:154K and is one of the three sublineages. This variant was initially identified in December 2020 in India. The major attribute of this variant is reduction in neutralization process previously shown by EUA monoclonal antibody treatment[95].

d) Lambda (lineage C.37)-The Lambda variant was firstly identified in Peru in August 2020, and it spread around the world to almost 30 countries. Even in July 2021, scientists were unable to report whether this mutant is more infectious and its resistance towards vaccines[96].

3.2. Variant of concern

A variant that focuses the attention of scientific community comes under the category of variant of concern. This type of variant undergoes mutation thereby showing increased transmissibility, more severe health issues with increased hospitalizations or even causes death. The seriousness is significant because of reduction in neutralization process produced during later infection or vaccination. Another main trait of this variant is reduced diagnostic detection failure, effectiveness of treatments and vaccines[97].

The most commonly known characteristics of a variant of concern or interest are,

a) Corroboration of increase in transmissibility ability
b) Impact on diagnostic test targets, decreased effect of vaccines or treatments or therapies, decreased neutralization treatment by antibodies and increased disease severity.

The list of variants studied under this category by various federal agencies are identified.

a) Alpha (lineage B.1.1.7)-This variant was first detected in October 2020 in United Kingdom. This variant was also known as labelled as Alpha variant by the WHO and was known as lineage B.1.1.7. Another name given to this variant are VUI–02012/01, VOC-202012/01, 20I/501Y.V1, 20I (V1), 20B/501Y.V1, and 501Y.V1. This variant has shown 40–

 doi:10.20944/preprints202208.0204.v1

80% increased transmissibility rate, potentially increase in fatality rate, and increased degree of pathogenicity of virus. In the month of May 2021, this variant spread over 120 countries[98].

b) Delta (lineage B.1.617.2)-The Delta variant was first identified in India in October 2020. It is also known as 21A/S:478K, B.1.617.2, 21A, or G/452R.V3. In May 2021, British researchers announced this mutant as a variant of concern, because it propagates more rapidly than its original type of the virus and could be able to spread as speedily as Alpha variant. In June 2021, scientific community finds out another mutant of Delta, which is known as K417N mutation[99]. This variant raised the concern about the probability of decreased antibody treatments, reduced efficacy of vaccines, and even the risk of reinfection increased. This mutant is given another name known as "**Delta plus**" which is also known as Pango lineages (AY.1 and AY.2). The Ministry of Health and Family Welfare in India declared this "Delta plus" mutant as mutant or variant of Concern on 22 June, 2021.

Beta (lineage B.1.351)-This variant is also known as 501.V2 variant, 20H (V2), 20C/501Y.V2, VOC-20DEC-02, 501.V2, 20H/501Y.V2, 501Y.V2, or also called lineage B.1.351. This variant was initially identified in South Africa. Scientists declared that the occurrence of the mutant was quite greater among youth with lesser health problems[100, 101].

Gamma (lineage P.1)-This variant is known as Variant of Concern and was first identified in Tokyo on 6 January, 2021. Gamma variant also exhibited 2.2 times higher transmissibility. These variants have shown ability to infect adults as well as older beings. The fatality rate of this variant was found about 10–80% more lethal[102].

3.1. Variant of high consequences

This variant has shown clear evidence about preventive measures related to earlierly spreading mutants. The most known characteristics of a mutant of high consequence are ramifications on medical counter measures (MCM):

i. Diagnostics Failure
ii. Reduction in vaccine effectiveness
iii. Increased hospitalizations due to severity of disease

Currently no such variant is known with increased level of high consequences.

4. Strategies in tackling the virus

The different strategies being studied and employed to tackle the COVID-19 virus has been summarized in **Table 3**.

Table 3. Different strategies to tackle the virus.

Strategy	Mode of Action	Examples	Reference
Polymerase inhibitors	Allosteric inhibitors bind to the polymerase but not the active site and cause conformational changes that impair polymerase function	HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs); doravirine 1	[103]
Nanotherapeutics	Nanoparticles have been found to alter the pH of the respiratory epithelium and have virucidal activity against SARS-CoV-2	Ag nanoparticles	[104, 105]
	The liposome complex binds to receptor (ACE2) and it prevents the entrance of the virus to the host cell.	Pulmonary proteoliposomes	[106]

 doi:10.20944/preprints202208.0204.v1

Microfluidic disc-direct RTqPCR (dirRT-qPCR) assay	The swab samples are taken to detect SARS-CoV-2, influenza A and B viral RNA simultaneously. The entire process is completed in 1.5 h, and positive signals can be detected in 57 min.		[107]
Biocatalytic routes	The biocatalytic approach is used to build up a fragment that inhibits a protease enzyme.	Danoprevir, Ruxolitinib	[108]
Double-Barreled CRISPR Technology	The genome of the RNA virus is cleaved by introducing CRISPR-Cas13 system absolutely into the diseased host cell by choosing the endocytic method of the virus.	Cas13 RNA-guided RNA endonuclease	[109]
Biomaterials based approach	The biomaterials interact with immune cells and simultaneously deliver cargo to the lungs to avoid off-target effects	Poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), lipids	[110]
Mass spectrometry techniques	The techniques identify pathogens, and uncover markers associated with pathogenesis	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF/MS), Ultra-high-pressure liquid chromatography coupled high-resolution mass spectrometry (UHPLC–HRMS)	[111]

A number of efforts have been focused towards the creation of the vaccines against SARS-CoV-2[5, 112] shown in **Figure 12**. The vaccine which are under development are based upon live attenuated viruses, inactivated attenuated viruses, protein sub-unit, VLP, replicating or non- replicating viral vector, RNA, DNA and even nanoparticles having unique advantages and disadvantages[113] shown in **Table 3**. A number of vaccines have been developed to boost the immunogenicity via using adjuvant skills such as MF-59 (Novartis), AS03 (GSK), CpG 1018 (Dynavax), etc. are available for the vaccine development[114, 115]. Immune informatics approach is used for identifying SARS-CoV-2 vaccine contenders by detecting cytotoxic B-cell and T-cells in the disease-causing (viral) proteins.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

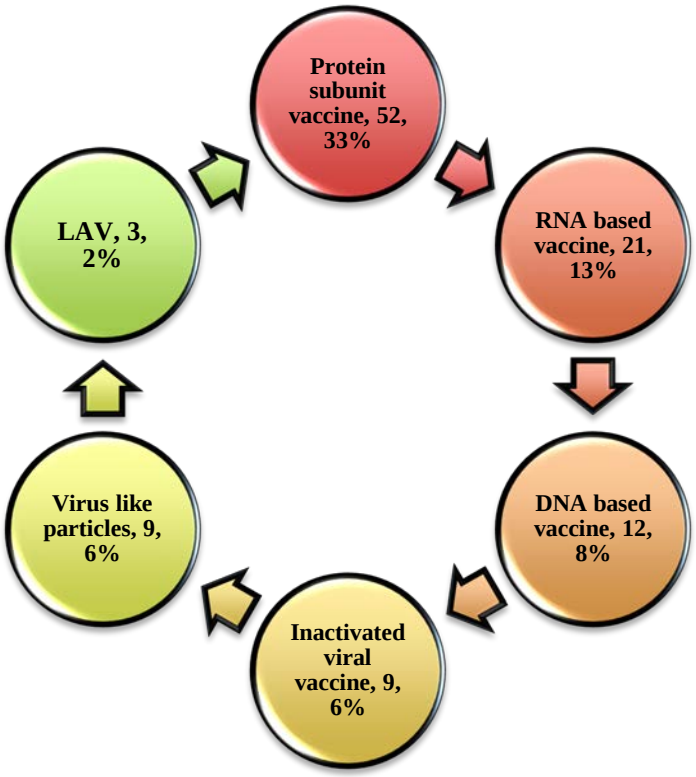


Figure 12. Schematic diagram representing different kinds of SARS-CoV-2 vaccines .

4.1. Protein subunit vaccine

Protein subunit vaccines are mostly constructed as synthetic peptides or recombinant antigenic proteins that are essentially used for long-term therapeutic or defensive immunity response. This type of subunit vaccine shows low immunogenicity and hence demands extra ancillary support to upraise the vaccine-induced immunity responses. This auxiliary support may progress the half-life (biological) of the antigen and also improves the immune-modulatory cytokine response[116, 117]. The addition of auxiliary subunit helps in reducing the inadequacies of the protein based vaccines. The S protein subunit of the SARS-CoV-2 virus is the utmost suitable antigen that induces antibodies versus the pathogen. These S Protein subunit comprises of two main subunits that includes S1 and S2 subunits. The S1 subunit has the RBD, NTD and RBM realms whereas S2 subunit consists of HR-1, HR-2 and FP realm. The antigenic fragments and its S-Protein subunits are the primary focuses for the establishment of the subunit vaccine[112, 118].

The numbers of vaccines produced via protein subunit methods are

i. **Novavax, Inc./ Emergent Bio-Solutions (NVX-CoV2373)-**This is a nanoparticle centered immunogenic vaccine that depends on the recombination of stable coronavirus S-protein (pre-fusion)[119].
ii. **Molecular Clamp Stabilized spike protein vaccine candidate-**This type of vaccine is established in collaboration between GSK and Dynavax. The developed vaccine is stable recombinant viral pre-fusion protein, tha stimulate the creation of neutralizing antibodies[120].
iii. **PittCoVacc** is a MNA or Micro-Needle Array based recombinant (SARS-CoV-2) vaccine, which includes the direction of recombinant immunogens (rSARS-CoV-2 S1 and rSARS-CoV-2-S1fRS09). An important upsurge in the antigen-based antibodies having statistical implication was seen in its preclinical trial models. Moreover, the vaccine immunogenicity was upheld due to sterilization by using gamma radiation[121].

 doi:10.20944/preprints202208.0204.v1

iv. **Triple antigen vaccine** is a VLP multi-antigenic type vaccine prototype in which the envelope protein, membrane, and the recombinant spike have been co-expressed in D-Crypt™ platform or *Saccharomyces cerevisiae* platform. In such vaccine, proteins undergo self-assembly as VLP. These types of prototype have ability to enter various pre-clinical trials. Additionally, it is supposed to be a safer and easier method for production of vaccines with cost-effective manner[122].

4.2. RNA based vaccines

The RNA based vaccines are manufactured by in-vitro transcription method and produces viral antigens in the cytoplasm via in vivo (direct protein) translation. It is an emergent, a non-integrating and non-infectious podium with no risk of mutagenesis. Mostly self-replicating and non-replicating RNAs are examined[123]. This immunogenicity can be minimalized, and the modifications made to form stable vaccines by permitting recurrent vaccine administration. This podium has inspired the development of vaccine because of its outstanding properties like capability to mimic and flexibility[124].

i. **Moderna TX, Inc (mRNA-1273)-T**his vaccine is constituted of synthetic mRNA encolsed in lipid based nanoparticle that contains pre-fusion stable spiked S-protein of SARS-CoV-2. It is known to be comparatively safer because it is neither made up of live pathogen nor inactivated pathogens[125].

ii. **BioNTech| FosunPharma| Pfizer (BNT162b1)-**It is known as codon-based mRNA vaccine. This vaccine encrypts trimerized SARS-CoV-2 RBD and the vaccine depicts an improved immunogenicity because of adding T4 fibritin-based trimerization field to the RBD antigen. This mRNA is enclosed in ionizable LNPs known as lipid based nanoparticles (80 nm) and cationic in nature that confirms its effective transport[126].

4.3. Viral vectored vaccines

The vaccine is a viral vector that is a capable for providing prophylactic treatment against a pathogen. This type of vaccine is extremely definite in carrying the respective genes to the target cells. This process is extremely capable in the transduction of gene and induces the immunity response[127, 128]. These produces high-level antigenic protein that finally leads to the removal of the virus infected cells.

i. **Ad5-nCoV (Beijing Institute of Biotechnology/ Can-Sino Biologics Inc.)-**Is a replication defective adenovirus type-5 vector (Ad5) that expresses the recombinant spike protein of SARS-CoV-2. This vaccine was synthesized by cloning of full-length S Protein gene and signal peptide gene (Plasminogen activator)[129].

ii. **Coroflu (FluGen | Bharat Biotech | University of Wisconsin-Madison)-** It is a self-limiting variety of the influenza that is tailored by addition of gene sequence of the spike protein of SARS-CoV-2 virus. Moreover, the vaccine articulates immunity response against the virus. This vaccine does not experience any replication because it scarcities of M2 gene. It can enter inside cell and hence encouraging vaccine against the virus. It is directed intra-nasally[114].

iii. **LV-SMENP-DC:** This vaccination is synthesized by engineering the lentiviral vector with dendritic cells. The vaccine subcutaneous inoculation confirms the presence of the antigens on antigen presenting cells, which finally activates the Cytotoxic T cells and afterward generates the immune response.

iv. **ChAdOx1:** is known as a recombinant adenovirus vaccine, which was prepared by using codon-based S glycoprotein and finally manufactured with the plasminogen activator (tPA) tissue. The sequence of SARS-CoV-2 contains coding for 2 to 1273 amino acids and the tPA and is transmitted in the

 doi:10.20944/preprints202208.0204.v1

shuttle plasmid. The plasmid is actually responsible for encrypting early human cytomegalovirus genes with TetO (tetracycline operator) sites and creation of BGH polyadenylation signal between the recombination-cloning sites[130].

4.3. DNA vaccines

The introduction of the DNA vaccine is the most revolutionary approach to vaccination that induces adaptive immune response. This trans-gene delivers a constant supply of particular proteins that is alike live virus. Moreover, the antigens are endocytosed by the immature DC (Dendritic Cells) that finally stimulates effective cell mediated as well as humoral immune responses[131].

INO-4800- It is a known as prophylactic DNA vaccine that is used against SARS-CoV-2. In this type, codon-based S protein sequence is attached with IgE leader. The IgE-spike SARS-CoV-2 sequence was prepared and then digested by using *BamHI* and *XhoI* and further incorporated inside the plasmid[132].

4.4. Live Attenuated Vaccines or LAV

The *DelNS1-SARS-CoV2-RBD* vaccine known LA vaccine is an influenza-based vaccination that strained with obliteration in the NS1 gene. This is restructured to specify the RBD domain on the surface of SARS-CoV-2 spike protein and is further cultured in the Madin Darby Canine Kidney Cells (MDCK) cells or chick embryo. The LA vaccines are highly immunogenic than wild influenza virus and can be administered as a nasal spray[133].

4.5. Virus-like particle vaccine

The vaccine contains self-assembled proteins capable of imitating the local viruses conformation with a dearth of viral genome. The VLP vaccines in comparison to protein vaccines are more akin to the local virus that leads to enhanced immune responses[134].

4.6. Inactivated viral vaccines

The vaccine is chemical based or radiation based inactivated virions. They constitute immunogenic constituents of novel virus and does not show reactivation property after inactivation of virus. In the case of inactivated viruses, immunogenic determinants are structurally mutilated because of inactivation method[135]. The example of inactivated viral vaccine is UV- and formaldehyde-inactivated SARS-CoV-2 that shows inducing property by neutralizing antibody response, and the clinical trial of phase I using β-propiolactone inactivated SARS-CoV-2 vaccine proved safe and can produce SARS-CoV-2 specific neutralizing antibodies[136, 137].

5. Chemistry in the combat of virus

The progress in therapeutics research for identified coronaviruses is becoming an active investigation area. Morse et al.[138] discussed about prevention and treatment selections for severe acute respiratory infections caused by novel CoV-19 virus. The four critical enzymes required for pathogenesis of virus are Spike protein, RNA dependent RNA polymerase, 3CLpro and PLpro. The spike protein accelerates entry of virus through the host cell. The two-protease enzymes known are the papain-like protease PLpro and 3CLpro that depicted the assembly of new virions, and finally the RdRp (RNA-dependent RNA polymerase) that helps in facilitating replication of the genome of CoV-RNA.

5.1. Targeting spike protein

A group of scientists predicted that COVID-19 receptor-binding domain (RBD) or spike binding site focus specifically towards the GRP78 (Glucose Regulated Protein 78) of the host cell-surface receptor by devoting the potential of structural bioinformatics in

 doi:10.20944/preprints202208.0204.v1

amalgamation with protein-protein docking. The homology model was developed first by using template of SARS-CoV-2 spike (PDB: 6ACD, chain C). After that structural alignments of SARS-CoV-2 spike with the Pep42 cyclic peptide was imagined. The HADDOCK software was used to demonstrate about protein-protein docking and the results confirmed the occurrence and usage of SBD b (substrate binding domain b). It also helps to identify host cell receptor of receptor-binding domain of the spike protein (SARS-CoV-2) [139, 140].

Chen and his co-workers proposed exceptional structural descriptions of the glycoprotein RBD spike. The RBD have ternary structure, which contains about 72% amino acid sequences. From molecular modeling results, it is revealed that phenylalanine (Phe486) moiety was found in the flexible loop implicates the diffusion of Phe486 into ACE2 deep hydrophobic pocket. This inspection may partially lead to stronger bonding between ACE2 of host cell and SARS-CoV-2[141].

Robson et al.[142] implemented another bioinformatics studies that are used to propose the interaction of synthetic vaccine and peptidomimetic contender against the SARS-CoV-2 spike glycoprotein. The researcher used Q-UEL language to accomplish its application in bioinformatics. The observed sequence motif was KRSFIEDLLFNKV, which relates to the acknowledged cleavage site of SARS. This sequence helps in formation of the basis for design of peptidomimetic agent and specific synthetic vaccine epitope.

5.2. Targeting N protein

Sarma et al. [143] discovered basically two probable inhibitors (ZINC000000146942 and ZINC000003118440) for binding of RNA to the N-terminal domain of Nucleo-capsid protein or N protein by using molecular modeling study. The authors studied two N-terminal domain arrangements of N proteins known as 1SSK and 2OFZ. Primarily, a fixed set of mixtures of compounds from Maybridge and Asinex library were collected out of which 15 compounds were selected with noteworthy docking scores. Thereafter, a number of studies have been performed to screen the compound named as Qik-Prop (pharmacokinetic properties) and SwissADME (drug-likeness). Another known compound of N-protein is theophylline derivative, which is usually known as a bronchodilator. These results confirmed that screened bronchodilators were approved against the RNA binding sites of N protein of CoVID-19. These permitted bronchodilators revealed the binding affinity of MM-GBSA in the order of:

Formeterol > Terbutaline > Ipratropium bromide > Tiotropium Bromide > Theophylline > Salbutamol

Currently, the protein-protein interactions (PPIs) were focused as a target for screening of structure-based small molecule. It was mostly used as an alternative drug design pattern that hasten the detection of antiviral drug against various pathogens[144]. The allosteric steadiness of PPIs of nucleocapsid resulted abnormal oligomerization of protein and it ultimately led to the decrease in viral activities. These results offer precious vision and motivations to researches for focusing on designing of non- native protein based antivirals[145].

5.3. Targeting E protein

The computational study is used to investigate the best-known arrangement of the E protein of SARS-CoV-2 present in PDB database shown by Gupta and his co-workers[146]. The structure of E protein is reported to be a penta-meric structured protein, which is composed of 35 alpha- helices and 40 loops. The SARS-CoV-2 E-protein docking study and various phytochemicals (Macaflavanone E, Belachinal, and Vibsanol) contain V25 as well as F26 amino acids that helps in finding of various binding interactions. The basic well-designed behavior of E protein after 200 ns disclosed that a-helix and E protein loop experience arbitrary movement, which modulates ion channel activity to support pathogenesis in humans.

 doi:10.20944/preprints202208.0204.v1

5.4. Targeting 3CLpro (Chymotrypsin-like protease)

The most commonly known three FDA-approved drugs are Remdesivir, Saquinavir, and Darunavir. The two known small molecules are flavone and coumarin derivatives, which behave as promising inhibitors of 3CLpro studied by Khan et al.[147]. The binding interaction in between the selected compounds and the active site residue of 3CLpro were significantly examined by utilizing the PLIF module in MOE (Molecular Operating Environment) software. The calculation of binding free energy and MD simulation were noted to estimate the steadiness of protein- ligand contact, dynamic behaviour, and binding affinity.

Kandeel and Al-Nazawi [148] described statistics of chief protease (Mpro) of CoVs sequence. A primary virtual screening (VS) studies of FDA permitted various drugs against first resolved PDB: 6LU7 (SARS-CoV-2 Mpro crystal structure). The FDA sanctioned drugs are actually optimized by using software named as OPLS2005 (force field) Ligprep and similarly the protein was investigated by using Schrodinger Maestro software package (Schrodinger LLC, NY, USA) by using protein preparation module. The principal 20 FDA permitted known drugs were Aminosalicylate Sodium and Pyrazinamide (antituberculosis agents), Ribavirin (antiviral agent), Bemegride (CNS stimulant), Chromocarb (a vasoprotective), (+,-)- Octopamine HCl (adrenergic agonist), Vitamin B12, Triflusal (cardiovascular drug), Telbivudine (anti-hepatitis B virus), and Aminophylline (bronchodilator), Nicotinamide (vitamin), Methazolamide (used in glaucoma), Temozolomide (anticancer), Tioxolone (anti-acne agent), Cysteamine HCl (nephropathiccystinosis), Propylthiouracil (antithyroid agent), Amiloride hydrochloride (diuretic), Methoxamine hydrochloride (alphaadrenergic agonist), and Zonisamide (anticonvulsant) [149].

5.5. Targeting RdRp (RNA dependent RNA polymerase)

A researcher from Egypt used automated homology modelling web server for executing homological modelling of RdRp SARS-CoV-2 [149]. Additional, molecular docking was exhibited to study Ribavirin, Sofosbuvir, IDX-184, and Remidisvir against COVID-19 RdRp. After docking it is advised that Ribavirin, Sofosbuvir, and IDX-184 could strongly bind to RdRp of SARS-CoV-2 and its interaction with Guanosine (IDX-184) derivative, Sofosbuvir, and Ribavirin with RdRp is found to be multiple hydrogen bonding. The IDX-184 and Sofosbuvir form interaction with metals for instance, Mg^{+2} with D652 and E702. The viral eradication occurs when IDX-184, which is Guanosine derivative, forms a salt bridge with D514 that is used for the improved stabilization of interactions, whereas in case of Sofosbuvir, mainly two hydrophobic interactions with Y510 and D651 occur[150, 151].

6. Global distribution of different vaccine candidates and their challenges

Almost a dozen of vaccines has been sanctioned in several countries including Russia, the United Kingdom, China, and the United States. About three billion doses have been distributed worldwide. Countries such as Israel, the United States and Bahrain, have shown outstanding progress for immunizing people[152]. The vaccination in India has been held at a fast pace in various places, where new variants spread abruptly, and relaxation given from government led to raise alarm for occurrence of third wave of COVID-19. A framework is structured that helps in designing the mode of global vaccine distribution by selecting priority groups. Precisely, a framework is basically a practical documentation that assists the government about what should be done for immunizing people from different background.

6.1. Essential and Frontline workers

 doi:10.20944/preprints202208.0204.v1

Before releasing the vaccine for general population, government decided to vaccinate workers of essential services and frontline workers. The frontline workers category included respiratory therapists, pulmonologists some non-medical personnel like security workers, workers who clean and sanitize rooms, etc. Whereas, armed personnel, communication services (e.g., utilities) provider, pharmacists, and general healthcare workers were categorized under essential workers' category.

6.1. Health risk populations

After frontline warriors, the utmost priority is given firstly to members having high possibility of severe disease or even death if infected and secondly to the people with high risk of infection.

a) Priority given to the population of age group of 65 years and above who have the probability of high risk of infection because of in contact with frontline warriors.
b) Priority given to the people having some chronic disorders that finally increases the risk of infection due to lack of immunity.
c) Another group of people who comes under the health risk population category are adults, those working in congested atmospheres, such as college dormitories, childcare facilities, prisons, banks etc.

Based on the occurrence of global challenges for distribution of vaccine a number of approvals given are:

6.1. Diversifying various types of vaccines

The ability to protect different population and races, diversification of various types of vaccines must be done. The genetic background of crowd must be studied before vaccination, as it develops alterable immunity or sensitivity for person towards vaccine.

6.1. Use of adjuvants and boosters

Certain booster drugs may result strong immunity towards COVID-19, which helps in fighting against it even for months or years. A few adjuvant-based vaccines like protein-based vaccines are produced with increased efficiency to decrease antigen amount and reduced cost. The latest innovative group of COVID-19 vaccines (Pfizer and Moderna) uses encapsulated Lipid Nanoparticles (LNPs). These synthesized vaccines are responsible for breakdown of the transmission chain of SARS-CoV-2. Because of mutation of virus, scientists found that booster vaccine helps in improving the immunity by combining antibodies with vaccines[153].

6.1. Immune response towards SARS-CoV-2

New therapeutic or immunogenic targets have been developed to improve immune response of future vaccine. A study has been done that confirms that people infected with virus develop T cells and even neutralizing antibodies for recognizing virus. Researchers found that some individuals have tested COVID negative due to presence of antibodies that identify the virus and fight against it. Different immune responses in variety of people guide researchers for better vaccination strategy i.e., requirement of single dose or two doses of a vaccine[154].

The standardization of immunoassays is must for vaccine efficacy and several efforts have been made by NIBSIC, WHO, and CEPI in this regard.

Proper social distancing, use of sanitizers and **masks** must be followed as safety measure: this helps in reducing the rate of virus transmission before the discovery of a harmless or safe vaccine. Only less than 1% of patients have shown re-occurrence of infection, and can transmit excessive levels of the virus, even when they are asymptomatic[155].

 doi:10.20944/preprints202208.0204.v1

a) The **alliance between vaccine developers and regulatory authorities** must be transparent that would finally hasten vaccine production and its authorization or approval process.
b) The **data shared for vaccine development** must be correct which finally enhances the public confidence.
c) Government must organize number of **educational programs** that increases the trust of community and decrease suspicion towards vaccination.
d) A fair vaccination strategy must be followed with easy **accessibility and affordability**, which will make low-income countries population able to vaccinate themselves.
e) **The role of native or local leaders** to upsurge the trust in drugs or vaccines and related strategies, which will finally increases the confidence of society towards vaccination.

7. Mechanistic approach of vaccine against COVID-19 and variants

Vaccines are the keystones in the management of outbreak of infectious diseases and curbing the epidemic and pandemic risks. Vaccines include different type of components including antigens, stabilizers, adjuvants, antibiotics, and preservatives.

Antigen is a foreign material originated from the structure of virus carrying or disease-causing organisms and trigger protective immune response within the body when induced. Based on the antigen drugs or vaccines can be considered as[156, 157]:

Live-attenuated drugs or vaccines: are modified from the present or existing bacteria or virus and weakened but not causing illness.

Inactivated vaccine: is derived from the killed type of pathogens incapable of duplication but affecting illness.

Subunit drug or vaccine: is made up of minimal fraction bacteria or virus that could be protein subunit or polysaccharides, protein or VLPs self-assembled from these constituents.

Peptide-based drugs or vaccines: peptides are basic component of a protein subunit acknowledged by the immune system and the antigens designated above comprehend peptide epitopes.

Stabilizer: is used enhance the efficacy of vaccine during its storage. Some of the stabilizers used in the vaccine are magnesium chloride, magnesium sulphate, lactose and gelatin.

Adjuvant: is a stimulating agent that boosts the immunity towards the co-delivered antigen.

Antibiotics: are used in lower amount during the development phase of the vaccine to prevent the bacterial contagion during tissue culture cells where viruses actually grow.

Preservatives: are additional to multiple dose vaccines that prevent bacterial as well as fungal growth. They include thiomersal, formaldehyde, or phenol derivatives.

The fight against COVID-19 has seen a vast designing and development of vaccine at a fast pace. There have been more than 170 different vaccines in trials. The important thing is to understand how these vaccines work and protect us against diseases. The different vaccine candidates, which have been developed so far and those, which are under trial, all try to achieve immunity to virus and stop the transmission by motivating an immunity response towards antigen (i.e. a virus molecule). In COVID-19, the antigens are spike protein, which are present on the surface of the virus or infection used to invade the host cell.

There are four ways in which vaccines work depending on their categories, which are as follows.

7.1. Whole virus

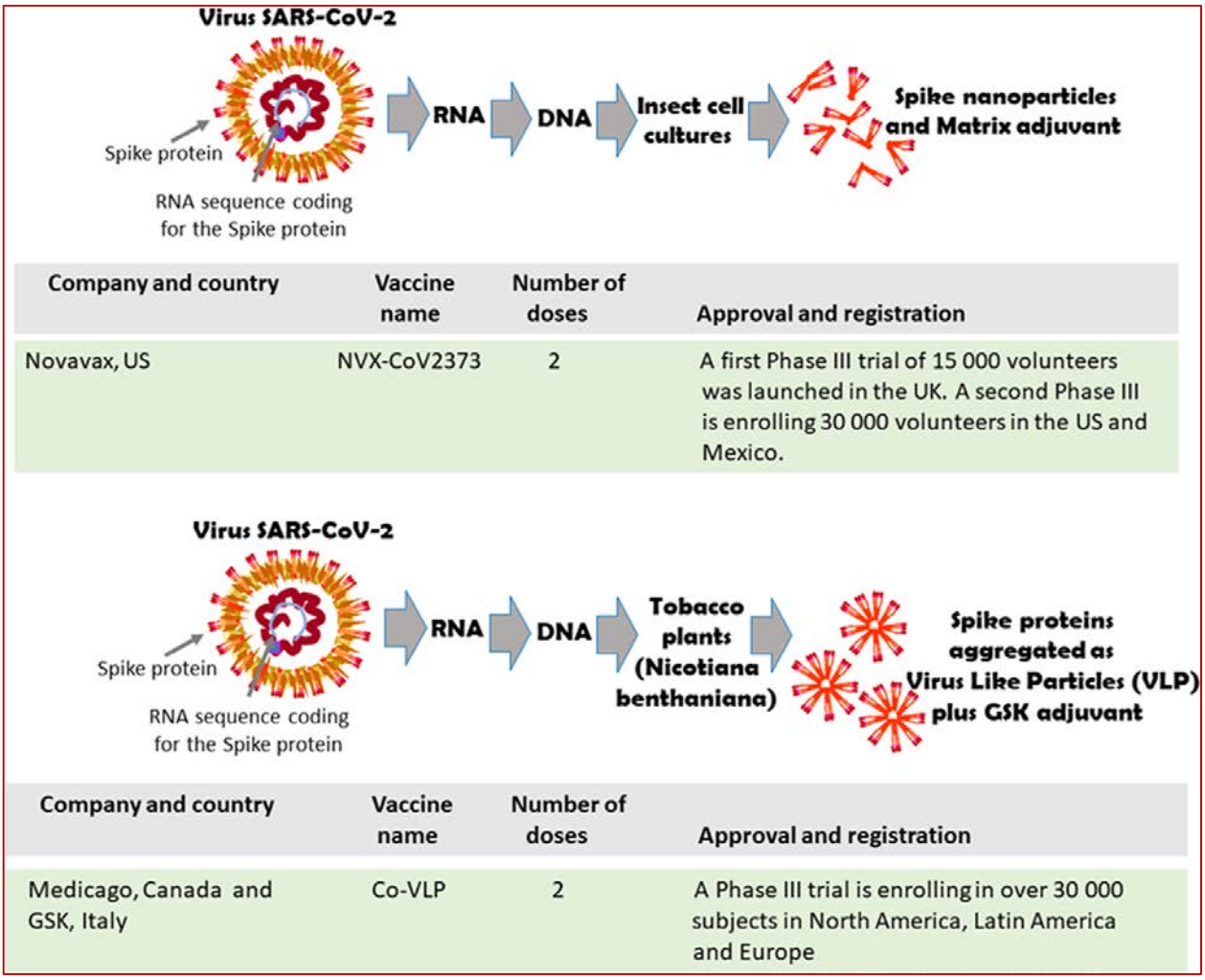
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

Most of the vaccines trigger an immune response to an antigen usually a spike protein found on the surface of the virus. Some traditional vaccines weaken or inactivate the virus so that once it is introduced inside the body; an immunity response could be produced to the antigen without disease causing virus. When the immunity response occurs, the T-cells or antibodies attack the virus and as a result the particular memory cells take comment of the particular antigen. The memory cells having chief immune response to generate cells and antibodies, which will mainly target the proteins. If the individual gets infected again with the similar virus, immune system gets ready to fight the virus off.

7.2. Protein subunit

The vaccine is designed by taking a fragment of the virus, for instance, spike protein to generate immune response. These have advantages as fragments are incapable of producing disease, are inexpensive to produce and relatively safe. However, these are least known or recognized by the immunity cells expected to attack infected cells and this may activate a weaker immunity response. Therefore, protein subunit vaccines contain adjuvant, which are designed to stimulate stronger immune response. Hepatitis B vaccine is one of the examples of protein subunit vaccine.

There have been numerous schemes based on SARS-CoV-2, their wreckages and at present there have been sixteen vaccine candidates in individual trials and two in phase II trial[158] (**Figure 13**).



Company and country	Vaccine name	Number of doses	Approval and registration
Novavax, US	NVX-CoV2373	2	A first Phase III trial of 15 000 volunteers was launched in the UK. A second Phase III is enrolling 30 000 volunteers in the US and Mexico.

Company and country	Vaccine name	Number of doses	Approval and registration
Medicago, Canada and GSK, Italy	Co-VLP	2	A Phase III trial is enrolling in over 30 000 subjects in North America, Latin America and Europe

Figure 13. Vaccine candidates using SARS-CoV-2 proteins or fragments in human trials and Phase II. Adapted from ref. 158.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0204.v1

7.2. Nucleic acids

The vaccines contain a genetic material either RNA or DNA to provide cells with the instructions to make to antigen. When the genetic material of the virus is injected inside the body, it uses the protein present in the cells to produce antigen that will generate an immune response. These vaccines mimic the way viruses normally reproduce during infection but rather than producing the copies of the virus, the cells only produce large amount of antigen thereby by triggering a stronger immune response. **Figure 14** shows the development of DNA based vaccine from the spike protein of SARS-CoV-2.

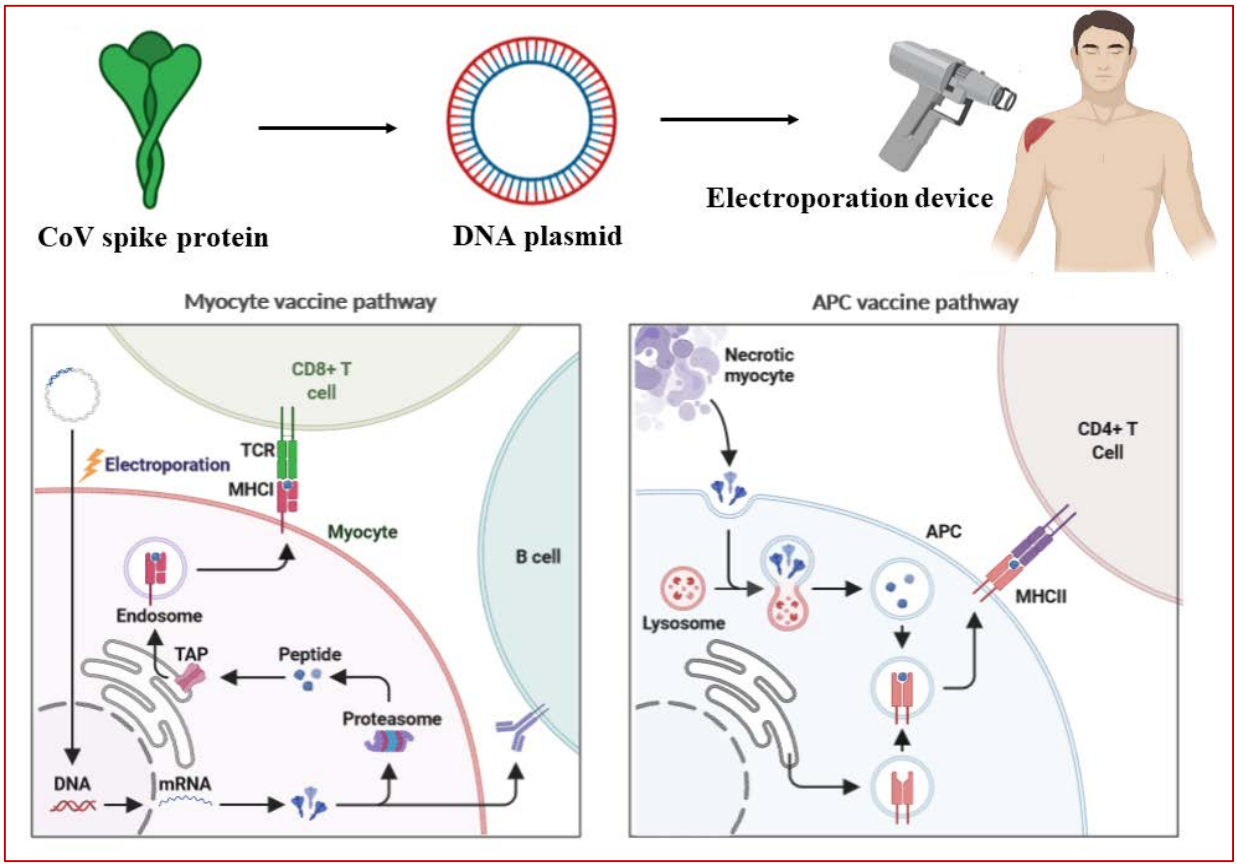


Figure 14. To make the DNA vaccine, the single-stranded RNA (ssRNA) of the SARS-CoV-2 coronavirus spike protein is extracted, synthesized into double-stranded (dsDNA), and cloned into a plasmid. This plasmid is then injected intramuscularly in conjunction with an electroporation device to facilitate uptake. Within the muscles, myocytes take up the plasmid and express the protein of interest. This will lead to either CD8+ T cell activation through MHC class I or B cell activation. Antigen presenting cells like macrophages will endocytose spike proteins from necrotizing myocytes and activate CD4+ T cells through MHC class II presentation. Overall, leading to the recruitment of multiple immune subsets.

7.2. Viral vector

The vaccine achieves immune response by inserting the genetic code for the antigen into a harmless virus which acts like a delivery system to get the code into the cells without causing the disease. Although vector-based vaccines are complicated to manufacture but they trigger a stronger immune response without the use of adjuvants. In this case one type of vector can be used to deliver code for the range of different antigens which can speed up vaccine development.

8. Future of cocktail of vaccine

In the current scenario, due to the shortage of supply of COVID 19 vaccine, many countries are testing to try out the mix and match of the vaccines. This is also known as heterologous vaccination regimen. The vaccines which have been approved require an

 doi:10.20944/preprints202208.0204.v1

interval of 8-12 weeks for administering the second dose after the first shot. Current COVID 19 production is not able to sufficiently cater the existing demand. Therefore, Canda, UK and countries in EU are looking to mix and match of Pfizer or Mederna vaccines. Spain, South Korea, Russia and China are also looking forward to have the 'cocktail 'of vaccines. Russia is planning to test the mix and match of Sputnik V and AstraZeneca. The CDC, US already allowed for the mixing of Pfizer and Moderna vaccines under 'exceptional circumstances' in January.

In June 2021, National Institute of Health (NIH) has started a Phase 1/2 clinical trial to give mixed booster doses of different COVID 19 vaccines to volunteers who have been fully vaccinated against COVID 19. This is done to counter the declining immunity and to keep the pace or step with the advancing variants of the virus. The trial involves around 150 persons who have used one of the three vaccines, Johnson & Johnson vaccine, Pfizer –BioNTech or Moderna vaccine. There will be a follow-up of all the trial participants for at least one year after getting the first vaccine or injection as a great part of the study. The results of the early trial are estimated in late summer 2021[159].

There are varied reasons to mix and match (cocktail) vaccines[160].

8.1. Potent immune response

A study known as 'CombivacS' conducted by researchers in Spain originate that vaccinating individuals with both the Pfizer–BioNTech and Oxford–AstraZeneca COVID-19 creates a powerful immunity response against the SARS-CoV-2 virus [161]. The study is the first in the world to provide the data on immunogenicity based on the combined use of two different vaccines. It is a Phase 2 clinical trial in which mixed dose of BioNtech / Pfizer has been administered to people under the age of 60. The first obtained results have indicated the enhanced immune response with no post vaccination severe side effects. A similar experimental has been conducted in UK (Com-COV). Although these results indicated that group of people who received mix-and-match of vaccine experienced side effects for instance fever which were not deemed severe.

8.2. Virus mutations and variants

The mix-and-match or cocktail of different vaccines might encourage the production of more antibodies thereby generating wider response against different emerging variants of the COVID-19. A study found that AstraZeneca is less effective against Delta variant, therefore, if a person is administered with another dose of a different vaccine then the body's immunity can be extended against more number of variants.

8.3. Limited production of vaccines

As the varaints are increasing, the number of COVID cases have also surged to the extend that the supply is not met with the demand in the market. Recently, there were sudden increase in the COVID cases in India and lot of deaths were seen. There was shortage of vaccine and in many parts of the country, government vaccination centres for those in the 18-44 age group closed due to limited supply of Covishield and Covaxin.

8.4. Safety issues

The use of AstraZeneca was halted in countries like Canada, UK, Germany and France due to the rare occurrence of blood clots in the younger age group. The use of cocktail of vaccination for immunization could be a plausible solution while ensuring safety.

Author Contributions: Conceptualization, D.S and N.S.; methodology, D.S and N.S.; validation, D.S and N.S.; formal analysis, D.S and N.S.; investigation D.S and N.S.; writing—original draft preparation, D.S., N.S. and S.K.; writing—review and editing, D.S., N.S., S.K and ST.; visualization, N.S.; supervision, S.K and ST. All authors have read and agreed to the published version of the manuscript.

Competing interests: The authors declare that they have no competing interests.

Acknowledgments: Our grateful acknowledgement goes to Biorender.com which was used to create the figures in the manuscript.

Reference

1. Li, Yingzhu, Rumiana Tenchov, Jeffrey Smoot, Cynthia Liu, Steven Watkins, and Qiongqiong Zhou. "A Comprehensive Review of the Global Efforts on Covid-19 Vaccine Development." *ACS Central Science* 7, no. 4 (2021): 512-33.
2. Babino, Andres, and Marcelo O. Magnasco. "Masks and Distancing During Covid-19: A Causal Framework for Imputing Value to Public-Health Interventions." *Scientific Reports* 11, no. 1 (2021): 5183.
3. Rothe, Camilla, Mirjam Schunk, Peter Sothmann, Gisela Bretzel, Guenter Froeschl, Claudia Wallrauch, Thorbjörn Zimmer, Verena Thiel, Christian Janke, Wolfgang Guggemos, Michael Seilmaier, Christian Drosten, Patrick Vollmar, Katrin Zwirglmaier, Sabine Zange, Roman Wölfel, and Michael Hoelscher. "Transmission of 2019-Ncov Infection from an Asymptomatic Contact in Germany." *New England Journal of Medicine* 382, no. 10 (2020): 970-71.
4. Pan, Xingfei, Dexiong Chen, Yong Xia, Xinwei Wu, Tangsheng Li, Xueting Ou, Liyang Zhou, and Jing Liu. "Asymptomatic Cases in a Family Cluster with Sars-Cov-2 Infection." *The Lancet Infectious Diseases* 20, no. 4 (2020): 410-11.
5. "Covid-19 Vaccine Tracker and Landscape." https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (
6. Noy-Porat, Tal, Efi Makdasi, Ron Alcalay, Adva Mechaly, Yinon Levy, Adi Bercovich-Kinori, Ayelet Zauberman, Hadas Tamir, Yfat Yahalom-Ronen, Ma'ayan Israeli, Eyal Epstein, Hagit Achdout, Sharon Melamed, Theodor Chitlaru, Shay Weiss, Eldar Peretz, Osnat Rosen, Nir Paran, Shmuel Yitzhaki, Shmuel C. Shapira, Tomer Israely, Ohad Mazor, and Ronit Rosenfeld. "A Panel of Human Neutralizing Mabs Targeting Sars-Cov-2 Spike at Multiple Epitopes." *Nature Communications* 11, no. 1 (2020): 4303.
7. Pomplun, Sebastian. "Targeting the Sars-Cov-2-Spike Protein: From Antibodies to Miniproteins and Peptides." *RSC Medicinal Chemistry* 12, no. 2 (2021): 197-202.
8. Piccoli, Luca, Young-Jun Park, M. Alejandra Tortorici, Nadine Czudnochowski, Alexandra C. Walls, Martina Beltramello, Chiara Silacci-Fregni, Dora Pinto, Laura E. Rosen, John E. Bowen, Oliver J. Acton, Stefano Jaconi, Barbara Guarino, Andrea Minola, Fabrizia Zatta, Nicole Sprugasci, Jessica Bassi, Alessia Peter, Anna De Marco, Jay C. Nix, Federico Mele, Sandra Jovic, Blanca Fernandez Rodriguez, Sneha V. Gupta, Feng Jin, Giovanni Piumatti, Giorgia Lo Presti, Alessandra Franzetti Pellanda, Maira Biggiogero, Maciej Tarkowski, Matteo S. Pizzuto, Elisabetta Cameroni, Colin Havenar-Daughton, Megan Smithey, David Hong, Valentino Lepori, Emiliano Albanese, Alessandro Ceschi, Enos Bernasconi, Luigia Elzi, Paolo Ferrari, Christian Garzoni, Agostino Riva, Gyorgy Snell, Federica Sallusto, Katja Fink, Herbert W. Virgin, Antonio Lanzavecchia, Davide Corti, and David Veesler. "Mapping Neutralizing and Immunodominant Sites on the Sars-Cov-2 Spike Receptor-Binding Domain by Structure-Guided High-Resolution Serology." *Cell* 183, no. 4 (2020): 1024-42.e21.

9. Liu, Sean T. H., Hung-Mo Lin, Ian Baine, Ania Wajnberg, Jeffrey P. Gumprecht, Farah Rahman, Denise Rodriguez, Pranai Tandon, Adel Bassily-Marcus, Jeffrey Bander, Charles Sanky, Amy Dupper, Allen Zheng, Freddy T. Nguyen, Fatima Amanat, Daniel Stadlbauer, Deena R. Altman, Benjamin K. Chen, Florian Krammer, Damodara Rao Mendu, Adolfo Firpo-Betancourt, Matthew A. Levin, Emilia Bagiella, Arturo Casadevall, Carlos Cordon-Cardo, Jeffrey S. Jhang, Suzanne A. Arinsburg, David L. Reich, Judith A. Aberg, and Nicole M. Bouvier. "Convalescent Plasma Treatment of Severe Covid-19: A Propensity Score–Matched Control Study." *Nature Medicine* 26, no. 11 (2020): 1708-13.
10. Kumar, Hemanth, and Surya Prakash. "A Review on Viral Infection Diseases." 2 (2017): 2455-698X.
11. Herrington, C. S., P. J. Coates, and W. P. Duprex. "Viruses and Disease: Emerging Concepts for Prevention, Diagnosis and Treatment." *J Pathol* 235, no. 2 (2015): 149-52.
12. Burrell, Christopher J., Colin R. Howard, and Frederick A. Murphy. "Pathogenesis of Virus Infections." *Fenner and White's Medical Virology* (2017): 77-104.
13. Kaslow, Richard A. "Epidemiology and Control: Principles, Practice and Programs." *Viral Infections of Humans: Epidemiology and Control* (2014): 3-38.
14. Legoff, Jérôme, Emmanuel Guérot, Angélique Ndjoyi-Mbiguino, Mathieu Matta, Ali Si-Mohamed, Laurent Gutmann, Jean-Yves Fagon, and Laurent Bélec. "High Prevalence of Respiratory Viral Infections in Patients Hospitalized in an Intensive Care Unit for Acute Respiratory Infections as Detected by Nucleic Acid-Based Assays." *Journal of clinical microbiology* 43, no. 1 (2005): 455-57.
15. Johnstone, J., S. R. Majumdar, J. D. Fox, and T. J. Marrie. "Viral Infection in Adults Hospitalized with Community-Acquired Pneumonia: Prevalence, Pathogens, and Presentation." *Chest* 134, no. 6 (2008): 1141-48.
16. Chi-Chung Cheng, Vincent, Jasper Fuk-Woo Chan, Ivan Fn Hung, and Kwok-Yung Yuen. "Viral Infections, an Overview with a Focus on Prevention of Transmission." *Reference Module in Biomedical Sciences* (2016): B978-0-12-801238-3.90174-0.
17. Grassly, Nicholas C., and Christophe Fraser. "Seasonal Infectious Disease Epidemiology." *Proceedings. Biological sciences* 273, no. 1600 (2006): 2541-50.
18. Alatoom, Adnan A, and D. Payne. "An Overview of Arboviruses and Bunyaviruses." *Labmedicine* 40 (2009): 237-40.
19. Díaz, A., R. Zaragoza, R. Granada, and M. Salavert. "Acute Viral Infections in Immunocompetent Patients." *Medicina Intensiva (English Edition)* 35, no. 3 (2011): 179-85.
20. Sauerbrei, A. "Herpes Genitalis: Diagnosis, Treatment and Prevention." *Geburtshilfe und Frauenheilkunde* 76, no. 12 (2016): 1310-17.
21. Wu, Y. P., D. D. Sun, Y. Wang, W. Liu, and J. Yang. "Herpes Simplex Virus Type 1 and Type 2 Infection Increases Atherosclerosis Risk: Evidence Based on a Meta-Analysis." *Biomed Res Int* 2016 (2016): 2630865.
22. Roy, C. J., and D. K. Milton. "Airborne Transmission of Communicable Infection--the Elusive Pathway." *N Engl J Med* 350, no. 17 (2004): 1710-2.
23. Gustafson, T. L., G. B. Lavely, E. R. Brawner, Jr., R. H. Hutcheson, Jr., P. F. Wright, and W. Schaffner. "An Outbreak of Airborne Nosocomial Varicella." *Pediatrics* 70, no. 4 (1982): 550-6.

24. Anderson, J. D., M. Bonner, D. W. Scheifele, and B. C. Schneider. "Lack of Nosocomial Spread of Varicella in a Pediatric Hospital with Negative Pressure Ventilated Patient Rooms." *Infect Control* 6, no. 3 (1985): 120-1.
25. Fugl, A., and C. L. Andersen. "Epstein-Barr Virus and Its Association with Disease - a Review of Relevance to General Practice." *BMC Fam Pract* 20, no. 1 (2019): 62.
26. Rostgaard, K., H. H. Balfour, Jr., R. Jarrett, C. Erikstrup, O. Pedersen, H. Ullum, L. P. Nielsen, M. Voldstedlund, and H. Hjalgrim. "Primary Epstein-Barr Virus Infection with and without Infectious Mononucleosis." *PLoS One* 14, no. 12 (2019): e0226436.
27. Boeckh, M., and A. P. Geballe. "Cytomegalovirus: Pathogen, Paradigm, and Puzzle." *J Clin Invest* 121, no. 5 (2011): 1673-80.
28. Al Mana, H., H. M. Yassine, N. N. Younes, A. Al-Mohannadi, D. W. Al-Sadeq, D. Alhababi, E. A. Nasser, and G. K. Nasrallah. "The Current Status of Cytomegalovirus (Cmv) Prevalence in the Mena Region: A Systematic Review." *Pathogens* 8, no. 4 (2019).
29. Wolz, Michael M., Gabriel F. Sciallis, and Mark R. Pittelkow. "Human Herpesviruses 6, 7, and 8 from a Dermatologic Perspective." *Mayo Clinic proceedings* 87, no. 10 (2012): 1004-14.
30. . In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*, edited by A. Arvin, G. Campadelli-Fiume, E. Mocarski, P. S. Moore, B. Roizman, R. Whitley and K. Yamanishi. Cambridge: Cambridge University Press

Copyright © Cambridge University Press 2007., 2007.

31. Angius, F., A. Ingianni, and R. Pompei. "Human Herpesvirus 8 and Host-Cell Interaction: Long-Lasting Physiological Modifications, Inflammation and Related Chronic Diseases." *Microorganisms* 8, no. 3 (2020).
32. Edelman, Daniel C. "Human Herpesvirus 8--a Novel Human Pathogen." *Virology journal* 2 (2005): 78-78.
33. Cheng, V. C., J. W. Tai, L. M. Wong, J. F. Chan, I. W. Li, K. K. To, I. F. Hung, K. H. Chan, P. L. Ho, and K. Y. Yuen. "Prevention of Nosocomial Transmission of Swine-Origin Pandemic Influenza Virus a/H1n1 by Infection Control Bundle." *J Hosp Infect* 74, no. 3 (2010): 271-7.
34. van der Sande, Marianne Ab, Adam Meijer, Fatmagül Sen-Kerpiclik, Remko Enserink, Herman Jm Cools, Piet Overduin, José M. Ferreira, and Marie-José Veldman-Ariessen. "Effectiveness of Post-Exposition Prophylaxis with Oseltamivir in Nursing Homes: A Randomised Controlled Trial over Four Seasons." *Emerging themes in epidemiology* 11 (2014): 13-13.
35. Cheng, V. C., J. W. Tai, W. M. Lee, W. M. Chan, S. C. Wong, J. H. Chen, R. W. Poon, K. K. To, J. F. Chan, P. L. Ho, K. H. Chan, and K. Y. Yuen. "Infection Control Preparedness for Human Infection with Influenza a H7n9 in Hong Kong." *Infect Control Hosp Epidemiol* 36, no. 1 (2015): 87-92.
36. Hall, C. B. "Nosocomial Respiratory Syncytial Virus Infections: The "Cold War" Has Not Ended." *Clin Infect Dis* 31, no. 2 (2000): 590-6.
37. Zawilińska, B., and M. Kosz-Vnenchak. "General Introduction into the Ebola Virus Biology and Disease." *Folia Med Cracov* 54, no. 3 (2014): 57-65.

38. Jacob, Shevin T., Ian Crozier, William A. Fischer, Angela Hewlett, Colleen S. Kraft, Marc-Antoine de La Vega, Moses J. Soka, Victoria Wahl, Anthony Griffiths, Laura Bollinger, and Jens H. Kuhn. "Ebola Virus Disease." *Nature Reviews Disease Primers* 6, no. 1 (2020): 13.
39. Goeijenbier, M., J. J. van Kampen, C. B. Reusken, M. P. Koopmans, and E. C. van Gorp. "Ebola Virus Disease: A Review on Epidemiology, Symptoms, Treatment and Pathogenesis." *Neth J Med* 72, no. 9 (2014): 442-8.
40. Lin, Kuan-Yin, Guan-Jhou Chen, Yu-Lin Lee, Yi-Chia Huang, Aristine Cheng, Hsin-Yun Sun, Sui-Yuan Chang, Chun-Eng Liu, and Chien-Ching Hung. "Hepatitis a Virus Infection and Hepatitis a Vaccination in Human Immunodeficiency Virus-Positive Patients: A Review." *World journal of gastroenterology* 23, no. 20 (2017): 3589-606.
41. Koenig, Kristi L., Siri Shastry, and Michael J. Burns. "Hepatitis a Virus: Essential Knowledge and a Novel Identify-Isolate-Inform Tool for Frontline Healthcare Providers." *The western journal of emergency medicine* 18, no. 6 (2017): 1000-07.
42. Noori, Navideh, John M. Drake, and Pejman Rohani. "Comparative Epidemiology of Poliovirus Transmission." *Scientific Reports* 7, no. 1 (2017): 17362.
43. Mehndiratta, M. M., P. Mehndiratta, and R. Pande. "Poliomyelitis: Historical Facts, Epidemiology, and Current Challenges in Eradication." *Neurohospitalist* 4, no. 4 (2014): 223-9.
44. Melnick, J. L. "Current Status of Poliovirus Infections." *Clinical microbiology reviews* 9, no. 3 (1996): 293-300.
45. Singh, R., K. P. Singh, S. Cherian, M. Saminathan, S. Kapoor, G. B. Manjunatha Reddy, S. Panda, and K. Dhama. "Rabies - epidemiology, Pathogenesis, Public Health Concerns and Advances in Diagnosis and Control: A Comprehensive Review." *Vet Q* 37, no. 1 (2017): 212-51.
46. Srinivasan, Krithika, Tim Kurz, Pradeep Kuttuva, and Chris Pearson. "Reorienting Rabies Research and Practice: Lessons from India." *Palgrave Communications* 5, no. 1 (2019): 152.
47. Fu, Z. F. "Rabies and Rabies Research: Past, Present and Future." *Vaccine* 15 Suppl (1997): S20-4.
48. Leyssen, P., E. De Clercq, and J. Neyts. "Perspectives for the Treatment of Infections with Flaviviridae." *Clinical microbiology reviews* 13, no. 1 (2000): 67-82.
49. Pierson, Theodore C., and Michael S. Diamond. "The Continued Threat of Emerging Flaviviruses." *Nature Microbiology* 5, no. 6 (2020): 796-812.
50. Tomori, O. "Yellow Fever: The Recurring Plague." *Crit Rev Clin Lab Sci* 41, no. 4 (2004): 391-427.
51. Owen, Robert L. "Yellow Fever : A Compilation of Various Publications Results of the Work of Maj. Walter Reed, Medical Corps, United States Army, and the Yellow Fever Commission / Presented by Mr. Owen." 0-0. Washington :: Govt. Print. Off, 1911.
52. Mackenzie, J. S., D. J. Gubler, and L. R. Petersen. "Emerging Flaviviruses: The Spread and Resurgence of Japanese Encephalitis, West Nile and Dengue Viruses." *Nat Med* 10, no. 12 Suppl (2004): S98-109.
53. Bartenschlager, R. "Molecular Targets in Inhibition of Hepatitis C Virus Replication." *Antiviral Chemistry and Chemotherapy* 8, no. 4 (1997): 281-301.

54. Alter, M. J., E. E. Mast, L. A. Moyer, and H. S. Margolis. "Hepatitis C." *Infect Dis Clin North Am* 12, no. 1 (1998): 13-26.
55. Turtle, L., and T. Solomon. "Japanese Encephalitis - the Prospects for New Treatments." *Nat Rev Neurol* 14, no. 5 (2018): 298-313.
56. Turtle, L., M. J. Griffiths, and T. Solomon. "Encephalitis Caused by Flaviviruses." *QJM : monthly journal of the Association of Physicians* 105, no. 3 (2012): 219-23.
57. Curren, E. J., N. P. Lindsey, M. Fischer, and S. L. Hills. "St. Louis Encephalitis Virus Disease in the United States, 2003-2017." *Am J Trop Med Hyg* 99, no. 4 (2018): 1074-79.
58. Enders, G. "Paramyxoviruses." In *Medical Microbiology*, edited by S. Baron. Galveston (TX): University of Texas Medical Branch at Galveston

Copyright © 1996, The University of Texas Medical Branch at Galveston., 1996.
59. Weinberg, G. A., C. B. Hall, M. K. Iwane, K. A. Poehling, K. M. Edwards, M. R. Griffin, M. A. Staat, A. T. Curns, D. D. Erdman, and P. G. Szilagyi. "Parainfluenza Virus Infection of Young Children: Estimates of the Population-Based Burden of Hospitalization." *J Pediatr* 154, no. 5 (2009): 694-9.
60. Kondamudi, N. P., and J. R. Waymack. "Measles." In *Statpearls*. Treasure Island (FL): StatPearls Publishing

Copyright © 2021, StatPearls Publishing LLC., 2021.
61. Fields, Bernard N., David M. Knipe, and Peter M. Howley. *Fields Virology*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013.
62. Parkman, P. D. "Biological Characteristics of Rubella Virus." *Arch Gesamte Virusforsch* 16 (1965): 401-11.
63. Zhang, R., C. F. Hryc, Y. Cong, X. Liu, J. Jakana, R. Gorchakov, M. L. Baker, S. C. Weaver, and W. Chiu. "4.4 Å Cryo-Em Structure of an Enveloped Alphavirus Venezuelan Equine Encephalitis Virus." *Embo j* 30, no. 18 (2011): 3854-63.
64. Cloyd, M. W. "Human Retroviruses." In *Medical Microbiology*, edited by S. Baron. Galveston (TX): University of Texas Medical Branch at Galveston

Copyright © 1996, The University of Texas Medical Branch at Galveston., 1996.
65. Varmus, H. "Retroviruses." *Science* 240, no. 4858 (1988): 1427.
66. Lai, C. C., T. P. Shih, W. C. Ko, H. J. Tang, and P. R. Hsueh. "Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2) and Coronavirus Disease-2019 (Covid-19): The Epidemic and the Challenges." *Int J Antimicrob Agents* 55, no. 3 (2020): 105924.
67. Pyrc, K., B. Berkhout, and L. van der Hoek. "Identification of New Human Coronaviruses." *Expert Rev Anti Infect Ther* 5, no. 2 (2007): 245-53.
68. Sandrock, C. E. "Severe Febrile Respiratory Illnesses as a Cause of Mass Critical Care." *Respir Care* 53, no. 1 (2008): 40-53; discussion 53-7.
69. Beigel, J. H. "Influenza." *Crit Care Med* 36, no. 9 (2008): 2660-6.
70. Couch, R. B. "Orthomyxoviruses." In *Medical Microbiology*, edited by S. Baron. Galveston (TX): University of Texas Medical Branch at Galveston

Copyright © 1996, The University of Texas Medical Branch at Galveston., 1996.

71. Arbeitskreis Blut, Untergruppe «Bewertung Blutassoziierter Krankheitserreger». "Influenza Virus." *Transfusion medicine and hemotherapy : offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie* 36, no. 1 (2009): 32-39.
72. Russell, C. J. "Orthomyxoviruses: Structure of Antigens." *Reference Module in Biomedical Sciences* (2016): B978-0-12-801238-3.95721-0.
73. Linster, M., L. A. H. Do, N. N. Q. Minh, Y. Chen, Z. Zhe, T. A. Tuan, H. M. Tuan, Y. C. F. Su, H. R. van Doorn, M. Moorthy, and G. J. D. Smith. "Clinical and Molecular Epidemiology of Human Parainfluenza Viruses 1-4 in Children from Viet Nam." *Sci Rep* 8, no. 1 (2018): 6833.
74. Henrickson, Kelly J. "Parainfluenza Viruses." *Clinical microbiology reviews* 16, no. 2 (2003): 242-64.
75. Falsey, Ann R. "Current Management of Parainfluenza Pneumonitis in Immunocompromised Patients: A Review." *Infection and drug resistance* 5 (2012): 121-27.
76. Hall, C. B. "Respiratory Syncytial Virus and Parainfluenza Virus." *N Engl J Med* 344, no. 25 (2001): 1917-28.
77. Manocha, S., K. R. Walley, and J. A. Russell. "Severe Acute Respiratory Distress Syndrome (Sars): A Critical Care Perspective." *Crit Care Med* 31, no. 11 (2003): 2684-92.
78. Bisht, Himani, Anjeanette Roberts, Leatrice Vogel, Alexander Bukreyev, Peter L. Collins, Brian R. Murphy, Kanta Subbarao, and Bernard Moss. "Severe Acute Respiratory Syndrome Coronavirus Spike Protein Expressed by Attenuated Vaccinia Virus Protectively Immunizes Mice." *Proceedings of the National Academy of Sciences of the United States of America* 101, no. 17 (2004): 6641.
79. Rota, P. A., M. S. Oberste, S. S. Monroe, W. A. Nix, R. Campagnoli, J. P. Icenogle, S. Peñaranda, B. Bankamp, K. Maher, M. H. Chen, S. Tong, A. Tamin, L. Lowe, M. Frace, J. L. DeRisi, Q. Chen, D. Wang, D. D. Erdman, T. C. Peret, C. Burns, T. G. Ksiazek, P. E. Rollin, A. Sanchez, S. Liffick, B. Holloway, J. Limor, K. McCaustland, M. Olsen-Rasmussen, R. Fouchier, S. Günther, A. D. Osterhaus, C. Drosten, M. A. Pallansch, L. J. Anderson, and W. J. Bellini. "Characterization of a Novel Coronavirus Associated with Severe Acute Respiratory Syndrome." *Science* 300, no. 5624 (2003): 1394-9.
80. Tripet, Brian, Megan W. Howard, Michael Jobling, Randall K. Holmes, Kathryn V. Holmes, and Robert S. Hodges. "Structural Characterization of the Sars-Coronavirus Spike S Fusion Protein Core." *The Journal of biological chemistry* 279, no. 20 (2004): 20836-49.
81. Sandrock, Christian, and Nicholas Stollenwerk. "Acute Febrile Respiratory Illness in the Icu: Reducing Disease Transmission." *Chest* 133, no. 5 (2008): 1221-31.
82. Wold, W. S., and K. Toth. "Adenovirus Vectors for Gene Therapy, Vaccination and Cancer Gene Therapy." *Curr Gene Ther* 13, no. 6 (2013): 421-33.
83. Danthinne, X., and M. J. Imperiale. "Production of First Generation Adenovirus Vectors: A Review." *Gene Therapy* 7, no. 20 (2000): 1707-14.
84. Muyangwa, Musalwa, Ekaterina V. Martynova, Svetlana F. Khaiboullina, Sergey P. Morzunov, and Albert A. Rizvanov. "Hantaviral Proteins: Structure, Functions, and Role in Hantavirus Infection." *Frontiers in microbiology* 6 (2015): 1326-26.
85. Battisti, A. J., Y. K. Chu, P. R. Chipman, B. Kaufmann, C. B. Jonsson, and M. G. Rossmann. "Structural Studies of Hantaan Virus." *J Virol* 85, no. 2 (2011): 835-41.

86. Lee, J. E., and E. O. Saphire. "Ebolavirus Glycoprotein Structure and Mechanism of Entry." *Future Virol* 4, no. 6 (2009): 621-35.
87. Beniac, Daniel, and Timothy Booth. "Structure of the Ebola Virus Glycoprotein Spike within the Virion Envelope at 11 Å Resolution." *Scientific Reports* 7 (2017): 46374.
88. McElroy, A. K., B. R. Erickson, T. D. Flietstra, P. E. Rollin, S. T. Nichol, J. S. Towner, and C. F. Spiropoulou. "Ebola Hemorrhagic Fever: Novel Biomarker Correlates of Clinical Outcome." *J Infect Dis* 210, no. 4 (2014): 558-66.
89. Mehedi, M., D. Falzarano, J. Seebach, X. Hu, M. S. Carpenter, H. J. Schnittler, and H. Feldmann. "A New Ebola Virus Nonstructural Glycoprotein Expressed through Rna Editing." *J Virol* 85, no. 11 (2011): 5406-14.
90. Ramadan, Nour, and Houssam Shaib. "Middle East Respiratory Syndrome Coronavirus (Mers-Cov): A Review." *Germs* 9, no. 1 (2019): 35-42.
91. McIntosh, Kenneth, M Hirsch, and A Thorner. "Middle East Respiratory Syndrome Coronavirus: Virology, Pathogenesis, and Epidemiology." 2016.
92. "Sars-Cov-2 Variant Classifications and Definitions." https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (
93. "Variants: Distribution of Case Data, 2 July 2021." (2021).
94. Jangra, S., C. Ye, R. Rathnasinghe, D. Stadlbauer, F. Krammer, V. Simon, L. Martinez-Sobrido, A. García-Sastre, and M. Schotsaert. "Sars-Cov-2 Spike E484k Mutation Reduces Antibody Neutralisation." *Lancet Microbe* 2, no. 7 (2021): e283-e84.
95. Greaney, Allison J., Andrea N. Loes, Katharine H. D. Crawford, Tyler N. Starr, Keara D. Malone, Helen Y. Chu, and Jesse D. Bloom. "Comprehensive Mapping of Mutations to the Sars-Cov-2 Receptor-Binding Domain That Affect Recognition by Polyclonal Human Serum Antibodies." *bioRxiv* (2021): 2020.12.31.425021.
96. "Tracking Sars-Cov-2 Variants." https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (
97. "Novavax Covid-19 Vaccine Demonstrates 89.3% Efficacy in Uk Phase 3 Trial." 2021.
98. Emary, Katherine, Tanya Golubchik, Parvinder Aley, Cristina Ariani, Brian Angus, Sagida Bibi, Beth Blane, David Bonsall, Paola Cicconi, Sue Charlton, Elizabeth Clutterbuck, Andrea Collins, Tony Cox, Thomas Darton, Christina Dold, Alexander Douglas, Christopher Duncan, Katie Ewer, Amy Flaxman, and Alexander Tarr. "Efficacy of Chadox1 Ncov-19 (Azd1222) Vaccine against Sars-Cov-2 Variant of Concern 202012/01 (B.1.1.7): An Exploratory Analysis of a Randomised Controlled Trial." *The Lancet* 397 (2021).
99. Deng, X., M. A. Garcia-Knight, M. M. Khalid, V. Servellita, C. Wang, M. K. Morris, A. Sotomayor-González, D. R. Glasner, K. R. Reyes, A. S. Gliwa, N. P. Reddy, C. Sanchez San Martin, S. Federman, J. Cheng, J. Balcerek, J. Taylor, J. A. Streithorst, S. Miller, G. R. Kumar, B. Sreekumar, P. Y. Chen, U. Schulze-Gahmen, T. Y. Taha, J. Hayashi, C. R. Simoneau, S. McMahon, P. V. Lidsky, Y. Xiao, P. Hemarajata, N. M. Green, A. Espinosa, C. Kath, M. Haw, J. Bell, J. K. Hacker, C. Hanson, D. A. Wadford, C. Anaya, D. Ferguson, L. F. Lareau, P. A. Frankino, H. Shivram, S. K. Wyman, M. Ott, R. Andino, and C. Y. Chiu. "Transmission, Infectivity, and Antibody Neutralization of an Emerging Sars-Cov-2 Variant in California Carrying a L452r Spike Protein Mutation." *medRxiv* (2021).

100. Liu, Yang, Jianying Liu, Hongjie Xia, Xianwen Zhang, Camila R. Fontes-Garfias, Kena A. Swanson, Hui Cai, Ritu Sarkar, Wei Chen, Mark Cutler, David Cooper, Scott C. Weaver, Alexander Muik, Ugur Sahin, Kathrin U. Jansen, Xuping Xie, Philip R. Dormitzer, and Pei-Yong Shi. "Neutralizing Activity of Bnt162b2-Elicited Serum." *New England Journal of Medicine* 384, no. 15 (2021): 1466-68.
101. Madhi, Shabir A., Vicky Baillie, Clare L. Cutland, Merryn Voysey, Anthonet L. Koen, Lee Fairlie, Sherman D. Padayachee, Keertan Dheda, Shaun L. Barnabas, Qasim Ebrahim Bhorat, Carmen Briner, Gaurav Kwatra, S. A. Ngs, Vida Covid team Wits, Khatija Ahmed, Parvinder Aley, Sutika Bhikha, Jinal N. Bhiman, As'ad Ebrahim Bhorat, Jeanine du Plessis, Aliasgar Esmail, Marisa Groenewald, Elizea Horne, Shi-Hsia Hwa, Aylin Jose, Teresa Lambe, Matt Laubscher, Mookho Malahleha, Masebole Masenya, Mduduzi Masilela, Shakeel McKenzie, Kgaogelo Molapo, Andrew Moultrie, Suzette Oelofse, Faeezah Patel, Sureshnee Pillay, Sarah Rhead, Hylton Rodel, Lindie Rossouw, Carol Taoushanis, Houriiyah Tegally, Asha Thombrayil, Samuel van Eck, Constantinos Kurt Wibmer, Nicholas M. Durham, Elizabeth J. Kelly, Tonya L. Villafana, Sarah Gilbert, Andrew J. Pollard, Tulio de Oliveira, Penny L. Moore, Alex Sigal, and Alane Izu. "Safety and Efficacy of the Chadox1 Ncov-19 (Azd1222) Covid-19 Vaccine against the B.1.351 Variant in South Africa." *medRxiv* (2021): 2021.02.10.21251247.
102. Wang, Pengfei, Maple Wang, Jian Yu, Gabriele Cerutti, Manoj S. Nair, Yaoxing Huang, Peter D. Kwong, Lawrence Shapiro, and David D. Ho. "Increased Resistance of Sars-Cov-2 Variant P.1 to Antibody Neutralization." *bioRxiv* (2021): 2021.03.01.433466.
103. Adamson, Catherine S., Kelly Chibale, Rebecca J. M. Goss, Marcel Jaspars, David J. Newman, and Rosemary A. Dorrington. "Antiviral Drug Discovery: Preparing for the Next Pandemic." *Chemical Society Reviews* 50, no. 6 (2021): 3647-55.
104. Dr. Subhasish, Sarkar. "Silver Nanoparticles with Bronchodilators through Nebulisation to Treat Covid 19 Patients." *Journal of Current Medical Research and Opinion* 3, no. 04 (2020).
105. Pandey, Abhijeet, Ajinkya N. Nikam, Sadhana P. Mutalik, Gasper Fernandes, Ajjappla Basavaraj Shreya, Bharath Singh Padya, Ruchira Raychaudhuri, Sanjay Kulkarni, Ruth Prassl, Suresh Subramanian, Aruna Korde, and Srinivas Mutalik. "Architectured Therapeutic and Diagnostic Nanoplatforms for Combating Sars-Cov-2: Role of Inorganic, Organic, and Radioactive Materials." *ACS Biomaterials Science & Engineering* 7, no. 1 (2021): 31-54.
106. Feliciello, I., and A. Procino. "The Pulmonary-Proteoliposome as a New Therapeutic Approach for Coronaviruses." *Hum Vaccin Immunother* 16, no. 10 (2020): 2373.
107. Ji, Minghui, Yun Xia, Jacky Fong-Chuen Loo, Lang Li, Ho-Pui Ho, Jianan He, and Dayong Gu. "Automated Multiplex Nucleic Acid Tests for Rapid Detection of Sars-Cov-2, Influenza a and B Infection with Direct Reverse-Transcription Quantitative Pcr (Dirrt-Qpcr) Assay in a Centrifugal Microfluidic Platform." *RSC Advances* 10, no. 56 (2020): 34088-98.
108. Slagman, Sjoerd, and Wolf-Dieter Fessner. "Biocatalytic Routes to Anti-Viral Agents and Their Synthetic Intermediates." *Chemical Society Reviews* 50, no. 3 (2021): 1968-2009.
109. Nalawansha, Dhanusha A., and Kusal T. G. Samarasinghe. "Double-Barreled Crispr Technology as a Novel Treatment Strategy for Covid-19." *ACS Pharmacology & Translational Science* 3, no. 5 (2020): 790-800.

110. Jarai, Bader M., Zachary Stillman, Kartik Bomb, April M. Kloxin, and Catherine A. Fromen. "Biomaterials-Based Opportunities to Engineer the Pulmonary Host Immune Response in Covid-19." *ACS Biomaterials Science & Engineering* 7, no. 5 (2021): 1742-64.
111. Mahmud, Iqbal, and Timothy J. Garrett. "Mass Spectrometry Techniques in Emerging Pathogens Studies: Covid-19 Perspectives." *Journal of the American Society for Mass Spectrometry* 31, no. 10 (2020): 2013-24.
112. Dhama, K., K. Sharun, R. Tiwari, M. Dadar, Y. S. Malik, K. P. Singh, and W. Chaicumpa. "Covid-19, an Emerging Coronavirus Infection: Advances and Prospects in Designing and Developing Vaccines, Immunotherapeutics, and Therapeutics." *Hum Vaccin Immunother* 16, no. 6 (2020): 1232-38.
113. Wang, Ning, Jian Shang, Shibo Jiang, and Lanying Du. "Subunit Vaccines against Emerging Pathogenic Human Coronaviruses." *Frontiers in microbiology* 11, no. 298 (2020).
114. Thanh Le, T., Z. Andreadakis, A. Kumar, R. Gómez Román, S. Tollefsen, M. Saville, and S. Mayhew. "The Covid-19 Vaccine Development Landscape." *Nat Rev Drug Discov* 19, no. 5 (2020): 305-06.
115. Baruah, V., and S. Bose. "Immunoinformatics-Aided Identification of T Cell and B Cell Epitopes in the Surface Glycoprotein of 2019-Ncov." *J Med Virol* 92, no. 5 (2020): 495-500.
116. Cao, Yan, Xiaoyue Zhu, Md Nazir Hossen, Prateek Kakar, Yiwen Zhao, and Xinyuan Chen. "Augmentation of Vaccine-Induced Humoral and Cellular Immunity by a Physical Radiofrequency Adjuvant." *Nature Communications* 9, no. 1 (2018): 3695.
117. Ou, Xiuyuan, Yan Liu, Xiaobo Lei, Pei Li, Dan Mi, Lili Ren, Li Guo, Ruixuan Guo, Ting Chen, Jiaxin Hu, Zichun Xiang, Zhixia Mu, Xing Chen, Jieyong Chen, Keping Hu, Qi Jin, Jianwei Wang, and Zhaohui Qian. "Characterization of Spike Glycoprotein of Sars-Cov-2 on Virus Entry and Its Immune Cross-Reactivity with Sars-Cov." *Nature Communications* 11, no. 1 (2020): 1620.
118. Graham, Barney S. "Rapid Covid-19 Vaccine Development." *Science* 368, no. 6494 (2020): 945.
119. "Novavax to Commence Human Trial for Covid-19 Vaccine." Clinical Trials Arena, 2020.
120. Tu, Yung-Fang, Chian-Shiu Chien, Aliaksandr A. Yarmishyn, Yi-Ying Lin, Yung-Hung Luo, Yi-Tsung Lin, Wei-Yi Lai, De-Ming Yang, Shih-Jie Chou, Yi-Ping Yang, Mong-Lien Wang, and Shih-Hwa Chiou. "A Review of Sars-Cov-2 and the Ongoing Clinical Trials." *International journal of molecular sciences* 21, no. 7 (2020): 2657.
121. Kim, E., G. Erdos, S. Huang, T. W. Kenniston, S. C. Balmert, C. D. Carey, V. S. Raj, M. W. Epperly, W. B. Klimstra, B. L. Haagmans, E. Korkmaz, L. D. Falo, Jr., and A. Gambotto. "Microneedle Array Delivered Recombinant Coronavirus Vaccines: Immunogenicity and Rapid Translational Development." *EBioMedicine* 55 (2020): 102743.
122. Arora, Kajal, Ruchir Rastogi, Nupur Mehrotra Arora, Deepak Parashar, Jeny Paliwal, Aelia Naqvi, Apoorva Srivastava, Sudhir Kumar Singh, Sriganesh Kalyanaraman, Swaroop Potdar, Devanand Kumar, Vidya Bhushan Arya, Sarthi Bansal, Satabdi Rautray, Indrajeet Singh, Pankaj Surendra Fengade, Bibekanand Kumar, and Prabuddha Kumar Kundu. "Multi-Antigenic Virus-Like Particle of Sars Cov-2 Produced in ≪Em≫Saccharomyces Cerevisiae≪/Em≫ as a Vaccine Candidate." *bioRxiv* (2020): 2020.05.18.099234.

123. Mulligan, Mark J., Kirsten E. Lyke, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, Kathleen Neuzil, Vanessa Raabe, Ruth Bailey, Kena A. Swanson, Ping Li, Kenneth Koury, Warren Kalina, David Cooper, Camila Fontes-Garfias, Pei-Yong Shi, Özlem Türeci, Kristin R. Tompkins, Edward E. Walsh, Robert Frenck, Ann R. Falsey, Philip R. Dormitzer, William C. Gruber, Uğur Şahin, and Kathrin U. Jansen. "Phase 1/2 Study to Describe the Safety and Immunogenicity of a Covid-19 Rna Vaccine Candidate (Bnt162b1) in Adults 18 to 55 Years of Age: Interim Report." *medRxiv* (2020): 2020.06.30.20142570.
124. Kauffman, K. J., M. J. Webber, and D. G. Anderson. "Materials for Non-Viral Intracellular Delivery of Messenger Rna Therapeutics." *J Control Release* 240 (2016): 227-34.
125. "Safety and Immunogenicity Study of 2019-Ncov Vaccine (Mrna-1273) for Prophylaxis of Sars-Cov-2 Infection (Covid-19)." National Institute of Allergy and Infectious Diseases (NIAID) 2020.
126. Mulligan, Mark J., Kirsten E. Lyke, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, Kathleen Neuzil, Vanessa Raabe, Ruth Bailey, Kena A. Swanson, Ping Li, Kenneth Koury, Warren Kalina, David Cooper, Camila Fontes-Garfias, Pei-Yong Shi, Özlem Türeci, Kristin R. Tompkins, Edward E. Walsh, Robert Frenck, Ann R. Falsey, Philip R. Dormitzer, William C. Gruber, Uğur Şahin, and Kathrin U. Jansen. "Phase i/Ii Study of Covid-19 Rna Vaccine Bnt162b1 in Adults." *Nature* 586, no. 7830 (2020): 589-93.
127. Afrough, B., S. Dowall, and R. Hewson. "Emerging Viruses and Current Strategies for Vaccine Intervention." *Clinical and experimental immunology* 196, no. 2 (2019): 157-66.
128. Zhu, Feng-Cai, Xu-Hua Guan, Yu-Hua Li, Jian-Ying Huang, Tao Jiang, Li-Hua Hou, Jing-Xin Li, Bei-Fang Yang, Ling Wang, Wen-Juan Wang, Shi-Po Wu, Zhao Wang, Xiao-Hong Wu, Jun-Jie Xu, Zhe Zhang, Si-Yue Jia, Bu-Sen Wang, Yi Hu, Jing-Jing Liu, Jun Zhang, Xiao-Ai Qian, Qiong Li, Hong-Xing Pan, Hu-Dachuan Jiang, Peng Deng, Jin-Bo Gou, Xue-Wen Wang, Xing-Huan Wang, and Wei Chen. "Immunogenicity and Safety of a Recombinant Adenovirus Type-5-Vectored Covid-19 Vaccine in Healthy Adults Aged 18 Years or Older: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial." *The Lancet* 396, no. 10249 (2020): 479-88.
129. Akova, Murat, and Serhat Unal. "A Randomized, Double-Blind, Placebo-Controlled Phase Iii Clinical Trial to Evaluate the Efficacy and Safety of Sars-Cov-2 Vaccine (Inactivated, Vero Cell): A Structured Summary of a Study Protocol for a Randomised Controlled Trial." *Trials* 22, no. 1 (2021): 276.
130. van Doremalen, Neeltje, Teresa Lambe, Alexandra Spencer, Sandra Belij-Rammerstorfer, Jyothi N. Purushotham, Julia R. Port, Victoria A. Avanzato, Trenton Bushmaker, Amy Flaxman, Marta Ulaszewska, Friederike Feldmann, Elizabeth R. Allen, Hannah Sharpe, Jonathan Schulz, Myndi Holbrook, Atsushi Okumura, Kimberly Meade-White, Lizzette Pérez-Pérez, Nick J. Edwards, Daniel Wright, Cameron Bissett, Ciaran Gilbride, Brandi N. Williamson, Rebecca Rosenke, Dan Long, Alka Ishwarbhai, Reshma Kailath, Louisa Rose, Susan Morris, Claire Powers, Jamie Lovaglio, Patrick W. Hanley, Dana Scott, Greg Saturday, Emmie de Wit, Sarah C. Gilbert, and Vincent J. Munster. "Chadox1 ncov-19 Vaccine Prevents Sars-Cov-2 Pneumonia in Rhesus Macaques." *Nature* 586, no. 7830 (2020): 578-82.

131. Hobernik, D., and M. Bros. "DNA Vaccines-How Far from Clinical Use?" *International journal of molecular sciences* 19, no. 11 (2018).
132. Smith, Trevor R. F., Ami Patel, Stephanie Ramos, Dustin Elwood, Xizhou Zhu, Jian Yan, Ebony N. Gary, Susanne N. Walker, Katherine Schultheis, Mansi Purwar, Ziyang Xu, Jewell Walters, Pratik Bhojnagarwala, Maria Yang, Neethu Chokkalingam, Patrick Pezzoli, Elizabeth Parzych, Emma L. Reuschel, Arthur Doan, Nicholas Tursi, Miguel Vasquez, Jihae Choi, Edgar Tello-Ruiz, Igor Maricic, Mamadou A. Bah, Yuanhan Wu, Dinah Amante, Daniel H. Park, Yaya Dia, Ali Raza Ali, Faraz I. Zaidi, Alison Generotti, Kevin Y. Kim, Timothy A. Herring, Sophia Reeder, Viviane M. Andrade, Karen Buttigieg, Gan Zhao, Jiun-Ming Wu, Dan Li, Linlin Bao, Jiangning Liu, Wei Deng, Chuan Qin, Ami Shah Brown, Makan Khoshnejad, Nianshuang Wang, Jacqueline Chu, Daniel Wrapp, Jason S. McLellan, Kar Muthumani, Bin Wang, Miles W. Carroll, J. Joseph Kim, Jean Boyer, Daniel W. Kulp, Laurent M. P. F. Humeau, David B. Weiner, and Kate E. Broderick. "Immunogenicity of a DNA Vaccine Candidate for Covid-19." *Nature Communications* 11, no. 1 (2020): 2601.
133. "Hku Joins Global Partnership to Develop Covid-19 Vaccine." 2020.
134. Qian, Ciying, Xinlin Liu, Qin Xu, Zhiping Wang, Jie Chen, Tingting Li, Qingbing Zheng, Hai Yu, Ying Gu, Shaowei Li, and Ningshao Xia. "Recent Progress on the Versatility of Virus-Like Particles." *Vaccines* 8, no. 1 (2020): 139.
135. Bolles, M., D. Deming, K. Long, S. Agnihothram, A. Whitmore, M. Ferris, W. Funkhouser, L. Gralinski, A. Totura, M. Heise, and R. S. Baric. "A Double-Inactivated Severe Acute Respiratory Syndrome Coronavirus Vaccine Provides Incomplete Protection in Mice and Induces Increased Eosinophilic Proinflammatory Pulmonary Response Upon Challenge." *J Virol* 85, no. 23 (2011): 12201-15.
136. Qu, D., B. Zheng, X. Yao, Y. Guan, Z. H. Yuan, N. S. Zhong, L. W. Lu, J. P. Xie, and Y. M. Wen. "Intranasal Immunization with Inactivated Sars-Cov (Sars-Associated Coronavirus) Induced Local and Serum Antibodies in Mice." *Vaccine* 23, no. 7 (2005): 924-31.
137. Lin, J. T., J. S. Zhang, N. Su, J. G. Xu, N. Wang, J. T. Chen, X. Chen, Y. X. Liu, H. Gao, Y. P. Jia, Y. Liu, R. H. Sun, X. Wang, D. Z. Yu, R. Hai, Q. Gao, Y. Ning, H. X. Wang, M. C. Li, B. Kan, G. M. Dong, Q. An, Y. Q. Wang, J. Han, C. Qin, W. D. Yin, and X. P. Dongs. "Safety and Immunogenicity from a Phase I Trial of Inactivated Severe Acute Respiratory Syndrome Coronavirus Vaccine." *Antivir Ther* 12, no. 7 (2007): 1107-13.
138. Morse, J. S., T. Lalonde, S. Xu, and W. R. Liu. "Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-Ncov." *Chembiochem* 21, no. 5 (2020): 730-38.
139. Dong, Ning, Xuemei Yang, Lianwei Ye, Kaichao Chen, Edward Wai-Chi Chan, Mengsu Yang, and Sheng Chen. "Genomic and Protein Structure Modelling Analysis Depicts the Origin and Infectivity of 2019-Ncov, a New Coronavirus Which Caused a Pneumonia Outbreak in Wuhan, China." *bioRxiv* (2020): 2020.01.20.913368.
140. Holmes, K. V. "Sars Coronavirus: A New Challenge for Prevention and Therapy." *J Clin Invest* 111, no. 11 (2003): 1605-9.

141. Navas-Martín, S. R., and S. Weiss. "Coronavirus Replication and Pathogenesis: Implications for the Recent Outbreak of Severe Acute Respiratory Syndrome (Sars), and the Challenge for Vaccine Development." *J Neurovirol* 10, no. 2 (2004): 75-85.
142. Robson, B. "Computers and Viral Diseases. Preliminary Bioinformatics Studies on the Design of a Synthetic Vaccine and a Preventative Peptidomimetic Antagonist against the Sars-Cov-2 (2019-Ncov, Covid-19) Coronavirus." *Comput Biol Med* 119 (2020): 103670.
143. Sarma, P., N. Shekhar, M. Prajapat, P. Avti, H. Kaur, S. Kumar, S. Singh, H. Kumar, A. Prakash, D. P. Dhibar, and B. Medhi. "In-Silico Homology Assisted Identification of Inhibitor of Rna Binding against 2019-Ncov N-Protein (N Terminal Domain)." *J Biomol Struct Dyn* 39, no. 8 (2021): 2724-32.
144. Bosch, J. "Ppi Inhibitor and Stabilizer Development in Human Diseases." *Drug Discov Today Technol* 24 (2017): 3-9.
145. Sijbesma, Eline, Kenneth K. Hallenbeck, Seppe Leysen, Pim J. de Vink, Lukasz Skóra, Wolfgang Jahnke, Luc Brunsveld, Michelle R. Arkin, and Christian Ottmann. "Site-Directed Fragment-Based Screening for the Discovery of Protein–Protein Interaction Stabilizers." *Journal of the American Chemical Society* 141, no. 8 (2019): 3524-31.
146. Gupta, M. K., S. Vemula, R. Donde, G. Gouda, L. Behera, and R. Vadde. "In-Silico Approaches to Detect Inhibitors of the Human Severe Acute Respiratory Syndrome Coronavirus Envelope Protein Ion Channel." *J Biomol Struct Dyn* 39, no. 7 (2021): 2617-27.
147. Khan, S. A., K. Zia, S. Ashraf, R. Uddin, and Z. Ul-Haq. "Identification of Chymotrypsin-Like Protease Inhibitors of Sars-Cov-2 Via Integrated Computational Approach." *J Biomol Struct Dyn* 39, no. 7 (2021): 2607-16.
148. Kandeel, Mahmoud, and Mohammed Al-Nazawi. "Virtual Screening and Repurposing of Fda Approved Drugs against Covid-19 Main Protease." *Life Sciences* 251 (2020): 117627.
149. Shah, B., P. Modi, and S. R. Sagar. "In Silico Studies on Therapeutic Agents for Covid-19: Drug Repurposing Approach." *Life Sci* 252 (2020): 117652.
150. Letko, Michael, Andrea Marzi, and Vincent Munster. "Functional Assessment of Cell Entry and Receptor Usage for Sars-Cov-2 and Other Lineage B Betacoronaviruses." *Nature Microbiology* 5, no. 4 (2020): 562-69.
151. Elfiky, A. A. "Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against Sars-Cov-2 Rna Dependent Rna Polymerase (Rdrp): A Molecular Docking Study." *Life Sci* 253 (2020): 117592.
152. Lung, J., Y. S. Lin, Y. H. Yang, Y. L. Chou, L. H. Shu, Y. C. Cheng, H. T. Liu, and C. Y. Wu. "The Potential Chemical Structure of Anti-Sars-Cov-2 Rna-Dependent Rna Polymerase." *J Med Virol* 92, no. 6 (2020): 693-97.
153. Jecker, N. S., A. G. Wightman, and D. S. Diekema. "Prioritizing Frontline Workers During the Covid-19 Pandemic." *Am J Bioeth* 20, no. 7 (2020): 128-32.
154. Hall, V., S. Foulkes, A. Charlett, A. Atti, E. J. M. Monk, R. Simmons, E. Wellington, M. J. Cole, A. Saei, B. Oguti, K. Munro, S. Wallace, P. D. Kirwan, M. Shrotri, A. Vusirikala, S. Rokadiya, M. Kall, M. Zambon, M. Ramsay, T. Brooks, Siren Study Group, C. S. Brown, M. A. Chand, and S. Hopkins. "Do Antibody Positive Healthcare Workers Have Lower Sars-Cov-2 Infection Rates Than Antibody Negative Healthcare Workers? Large Multi-Centre

Prospective Cohort Study (the Siren Study), England: June to November 2020." *medRxiv* (2021): 2021.01.13.21249642.

155. Krammer, Florian, Komal Srivastava, Paris team the, and Viviana Simon. "Robust Spike Antibody Responses and Increased Reactogenicity in Seropositive Individuals after a Single Dose of Sars-Cov-2 Mrna Vaccine." *medRxiv* (2021): 2021.01.29.21250653.
156. Shin, Matthew D., Sourabh Shukla, Young Hun Chung, Veronique Beiss, Soo Khim Chan, Oscar A. Ortega-Rivera, David M. Wirth, Angela Chen, Markus Sack, Jonathan K. Pokorski, and Nicole F. Steinmetz. "Covid-19 Vaccine Development and a Potential Nanomaterial Path Forward." *Nature Nanotechnology* 15, no. 8 (2020): 646-55.
157. Damodharan, Kannan, Gandarvakottai Senthilkumar Arumugam, Suresh Ganesan, Mukesh Doble, and Sathiah Thennarasu. "A Comprehensive Overview of Vaccines Developed for Pandemic Viral Pathogens over the Past Two Decades Including Those in Clinical Trials for the Current Novel Sars-Cov-2." *RSC Advances* 11, no. 33 (2021): 20006-35.
158. Forni, Guido, Alberto Mantovani, Guido Forni, Alberto Mantovani, Lorenzo Moretta, Rino Rappuoli, Giovanni Rezza, Arnaldo Bagnasco, Giuseppina Barsacchi, Giovanni Bussolati, Massimo Cacciari, Pietro Cappuccinelli, Enzo Cheli, Renato Guarini, Massimo Livi Bacci, Marco Mancini, Cristina Marcuzzo, Maria Concetta Morrone, Giorgio Parisi, Gianfranco Pasquino, Carlo Patrono, Alberto Quadrio Curzio, Giuseppe Remuzzi, Alessando Roncaglia, Stefano Schiaffino, Paolo Vineis, and Rome on behalf of the Covid-19 Commission of Accademia Nazionale dei Lincei. "Covid-19 Vaccines: Where We Stand and Challenges Ahead." *Cell Death & Differentiation* 28, no. 2 (2021): 626-39.
159. "Nih Clinical Trial Evaluating Mixed Covid-19 Vaccine Schedules Begins." https://www.nih.gov/news-events/news-releases/nih-clinical-trial-evaluating-mixed-covid-19-vaccine-schedules-begins (
160. Raghavan, Prabha. "Explained: Mixing Covid-19 Vaccines." https://indianexpress.com/article/explained/india-mixing-covid-19-vaccines-7351680/ (
161. "Mix-and-Match Covid Vaccines Trigger Potent Immune Response." Nature, https://www.nature.com/articles/d41586-021-01359-3 (