ijlpr 2022; doi 10.22376/ijpbs/lpr.2022.12.1.L55-71

International Journal of Life science and Pharma Research

ISSN 2250-0480

Review Article

Covid –From Genetic makeup to vaccine

A review on covid-19: From molecular variability, drug development to status of vaccine clinical trials

Rimjhim Singh, Neha Bothra, Murali Mohan Challa* And Prameela Kandra

Department of Biotechnology, GITAM Institute of Technology, GITAM (Deemed to be University), Visakhapatnam – 530045.

Abstract: A pandemic has erupted in all parts of the globe, originating from Wuhan province in China in December 2019. The virus was evaluated from the Coronaviridae family and Co ronaviridae subfamily, which showed homology with another virus spread across the globe originating from China in November 2002. It also showed pneumonia-like symptoms and was known as Severe Acute Respiratory Syndrome (SARS). SARS CoV-2 is the new 2019 virus believed to show animal to human transmission and vice-versa. Many intermediate hosts should be included to be suitable for human receptors. Finally, the virus could have evolved due to RNA recombination in the high frequency of the significant result of the plastic genome underpinning all the evolutionary forces in CoVs. This resulted in the adaptation of various hosts by this virus due to different genotypes. In the genome, there are 6-10 ORFs. Starting 2/3rd of the genome codes for replicase protein and the part has a fixed order of structural protein genes as (HE)-S-E-M-N. In Human beings, the virus first infects respiratory systems and alveolar cells in the lungs. The cellular receptor for the SARS virus is angiotensin-converting enzyme2 (ACE2). The existing reviews mostly focus on specific areas of COVID19. This review gives a comprehensive phylogeny analysis and genetic makeup of the virus, making it a target site for scientists looking for a fair comparison. It provides brief information on mutation undergoing by the virus, various drugs being used and stages of drug development, vaccine development, and its administration across the world, side effects of the vaccine, which are currently trending topics. We concentrated mainly on diversifying our review and making it unique by covering all the required information. This review would be more beneficial to the researcher and a general reader to understand the COVID 19.

Keywords: Covid-19, Morphology, Molecular Mutations, drugs, clinical trials, vaccine, Drugs for Covid, Delta Variation, covid-19 syndrome.

***Corresponding Author**

Prof. Murali Mohan Challa , Department of Biotechnology, GITAM Institute of Technology, GITAM (Deemed to be University), Visakhapatnam – 530045.

Received On 28 September, 2021
Revised On 4 December, 2021
Accepted On 10 December, 2021
Published On 6 January, 2022

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Rimjhim Singh, Neha Bothra, Murali Mohan Challa*, Prameeela Kandra , A review on covid-19: from molecular variability, drug development to status of vaccine clinical trials.(2022).Int. J. Life Sci. Pharma Res.12(1), L55-71 http://dx.doi.org/10.22376/ijpbs/lpr.2022.12.1.L55-71

1. INTRODUCTION

During November 01, 2002, to July 31, 2003, the onset of pneumonia-like illness had spread from China to across the globe, known as a severe acute respiratory syndrome (SARS). It first appeared in Guangdong, Southern China. The symptoms of the disease included chills, myalgia, fever, and cough. In severe cases, especially at the old age group lymphopenia and liver dysfunction were also associated. In a study, it was found out that, out of 50 patients, 45 were infected by the virus belonging to Coronaviridae[1,2]. Histological changes in the patients with SARS included desquamation of pneumocytes, hyaline membrane formation, presence of syncytia, and enlarged pneumocytes, thickened alveolar walls and also find air space containing fibromyxoid organizing exudate in later stages. To diagnose any disease and reach an appropriate cure, one must first find the causative agent. In SARS, several agents have been proposed, which mainly included mycoplasma pneumonia and chlamydia sp., as the possible source. However, a thorough investigation rules out these possibilities, and a noble coronavirus was identified in patients with SARS [3]. A study of the first 10 cases was conducted after the disease outbreak in Canada among the age group of 24 to 78. Which included six men, 3 of them had type-2 diabetes, 2 had pulmonary disease, four patients had a smoking history. It was seen that the average estimated incubation time was about 3 to 10 days. In the virology examination of SARS-CoV-2, all the respiratory, stool, blood specimens showed negative results. In addition, the extraction of DNA and RNA in RT-PCR also showed negative results. However, nasopharyngeal swabs and bronco alveolar fluids were amplified using a primer for nestedRTPCR,whichis5'CTTTGGACTTAATGACAGATG3'and5'GTCTTCCTGTGCTAACTTTG3', showed positive result[4]. It was seen that 70.7% of the genome in the most prominent gene of SARS-CoV encodes polymerase. The spike gene is the next largest[5]. The virus that causes SARS also possess an RNA- genome with a linear plus sense strand, which has a 3' poly A-tail and 5' methylated cap, and the viral replicase is translated directly from the genomic sense strand RNA, which then creates the copy of the genomic RNA (minus-sense strand) and a set of sub-genomic, shorter mRNAs having a standard 3' UTRs. In the upstream of the 3' poly-A tail ,the 3' TRRs are shared with a 32- nucleotide SARS RNA, which is termed as stem-loop II motif (s2m) in astroviruses of humans. It is the highly conserved element of RNA in astroviruses and coronaviruses. It is essential to study the RNA element with a high degree of conservation for designing antiviral drugs or vaccines. Such a degree of conservation is also crucial for studying the evolution, replication, and growth of these viruses[6]. From the study of x-ray crystallography at 2.7- A^0 resolution, the structure divulges several novel tertiary interactions and a substantial 90° bend of the s2m RNA. Although this RNA is unique in structure, its backbone fold reveals that s2m RNA mimics the 530 loops of 16S rRNA. The binding of ribosomal 530 loops to proteins permits the hypothesis that in SARS, the role of s2m RNA also involves initiation of translation[6]. The review aims to cover all the required information right from the virus's origin to drug developments currently against it. It will prove to be a one-stop site for anyone looking for any information regarding the current pandemic. We showed the distribution pattern of the virus worldwide and the speed of vaccination drive in different countries along with covering the structure, life cycle, history, and future impacts of the virus. No other review published to date that has all the essential and trending topics covered in a single paper, which makes this review unique. Apart from delivering core information, the review also covers basic definitions for beginners. The language in the review is kept basic intentionally by the writers to let everyone engage effectively in the reading.

1.1 Origin of SARS-CoV and SARS-CoV-2

Generally, SARS is caused by a virus called SARS-CoV. SARS-CoV is a member of Coronaviridae family[7]. This Coronaviridae family belongs to a subfamily named Orthocoronaviridae. These are divided into four genera, i.e., Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus[8,9]. SARS-CoV firstly emerged in Guangdong, China, in 2002. Initially, it was assumed that Civets were the cause of SARS because it was isolated from Himalayan palm civets[10]. Still, the initial assumption that civets are the reservoir of SARS-CoV was a decline due to many reasons and observation[11]. Now the question arises of how this virus gets transferred from animal to humans or vice versa and humans to humans or animal to animal. Till now, this type of transmission or jumping is still not explained adequately. This can be due to a potential natural reservoir of the virus that can infect other animal species[12].After SARS-CoV, in 2012, an epidemic in Saudi Arabia called MERS (Middle East Respiratory Syndrome). In 2019, the world was hit by a new pandemic situation, and this disease resembled SARS. This disease is caused by a virus named SARS-CoV-2 or COVID-19 (Corona Virus Disease 2019) by WHO on February 11, 2020[14]. There are many theories for the origin of SARS-CoV-2. It is not likely to say, SL-CoV is manipulated in laboratories and produced SARS-CoV-2. As mentioned, ACE-2 is the site where the RBD of SARS-CoV-2, which binds in humans, is different from previously predicted. Also, if any manipulation of genes is done, then one of the many reverse genetically engineered systems of Betacoronavirus have been used. According to data, SARS-CoV-2 is not acquired from a previously studied virus. So, there can be two reasons for its origin, i.e., either before the zoonotic transfer, an animal host naturally selects it, or during zoonotic transfer, it is naturally selected by humans. After an epidemic in 2002/2003 and 2012, many laboratories conducted tests and research on these viruses under group 2 laboratories. According to theories, it is possible that SARS-CoV-2 can get mutated at RBD. SARS-CoV-2 has a similar coronavirus found in pangolins, and their RBDs are identical is proof that SARS-CoV-2 can be a result of recombination and mutation[15]

1.2 Phylogeny

Coronavirus belongs to Coronavirinae subfamily and Coronaviridae family and Nidovirales order. There is one other subfamily called Torovirinae. Coronaviruses are of four types (genus)- alphacoronavirus (B.1.1.7), Betacoronavirus (B.1.351), Gammacoronavirus (P.1), Deltacoronavirus (B.1.617.2). Betacoronavirus has four lineages, i.e., lineage a, b, c, and d. When the SARS-CoV virus affected the people and spread, only 10 coronaviruses with the entire genome were available. Then, after 2008 and 2016, coronaviruses with complete genomes got added to the list[16].

1.3 Morphological Characters of Virus

It is essential to understand coronavirus structure and its resemblance with other viruses and its phylogeny, mechanism of entering a tissue, mode of infection, and multiplication process.[14] Under an electron microscope, coronaviruses

appear to be in crown-like structure, so it is named as coronavirus[17]. They are spherical or sometimes pleomorphic, with a diameter ranging from 60 to 140 nm and a spike length of about 8 to 12 nm. These viruses are enveloped, derived from the host cell, and their size ranges from 80 to 120 nm. Their RNA is the longest among all RNA viruses. Their RNA genome is single and positive-stranded RNA with 5' capped and its length is somewhere between 26.2 to 31.7 kb[18]. Envelope has a surface like projection called spikes which are made up of glycoprotein. The nucleocapsid is either helical or spherical in shape when it is in relaxed or inside the virus, respectively. Nucleocapsid also protects the genome. Usually, replication of viral RNA is unique, and coronavirus RNA gets replicated in the host cell in the cytoplasm. A set of mRNAs are produced with the same 3' ends by continuous attachment and detachment of RNA polymerase with the primary sequence of viral genomic RNA coronavirus[17]. Genomic regions were suitable for targeting with rRT-PCR comprising the E, N, and RdRp genes. Diagnostic tests targeting these regions have been used for routine use in various hospital laboratories around the world[19]. In the genome, there are 6-10 ORFs. Starting 2/3rd of genome codes for replicase protein, the last part has a fixed order of structural protein genes (HE)-S-E-M-N. There are many other proteins encoded in ORF[18]. There are four to five structural proteins. They are as follows- Spike (S), Nucleocapsid (N), Envelope (E), Membrane (M), and Hemagglutinin-esterase (HE) proteins. This HE protein is an extra gene protein present in some virus-like HCoV-OC43 and HCoV-HKU1 coronavirus, whereas some of the viruses do not express this type of protein HCoV-229E, SARS-CoV-2, HCoV-NL63, and SARS-CoV[20].

1.4 Symptoms of SARS-CoV-2

There are many symptoms of this disease. Some are mild symptoms, whereas others are severe symptoms, and some of them even do not show any symptoms. So, some of the researchers from London had divided the virus based on symptom clusters and identified the severity of the case. Primarily, they had six different sets of symptoms.

1. Flu-like with no fever: In this type, symptoms include cough, headache, muscle pain, loss of smell, chest pain, sore throat. All of these symptoms but with no fever.
2. Flu-like with fever: Symptoms include loss of appetite, sore throat, headache, hoarseness, loss of smell, and fever.
3. Gastrointestinal: This includes headache, sore throat but no cough, chest pain, loss of appetite, diarrhoea, loss of smell.
4. Severity level 1, fatigue: The symptoms are fatigue, cough, and chest pain, and hoarseness, loss of smell, headache, and also fever[84].
5. Severity level 2, confusion: Symptoms are sore throat, cough, hoarseness, chest pain, muscle pain, fatigue, confusion, loss of appetite, headache, loss of smell, and fever.
6. Severity level 3, abdominal and respiratory: This includes headache, abdominal pain, loss of appetite, diarrhoea, loss of smell, and shortness of breath[81].

Patients with health issues like diabetes or lung diseases and old and fragile patients tend to have a high risk of severity in their case. So, after five days of their first symptoms experience, researchers' study and factorize the case based on sex, age, BMI, and study their patient's history reports with any pre-existing health conditions[20]. Persons who are immensely affected are treated with steroids which decreases the immunity of a person and that further leads to attack by many dreadful bacteria and fungus-like black, white, and yellow as seen in India during their Second wave.

1.4.1 Post Covid 19 syndrome[88]

Even after recovering from covid-19, people see certain persistent symptoms. A similar pattern was also observed in people effected with SARS and MERS. Few of the syndromes Are discussed below

Cardiovascular sequelae

It includes palpitations, dyspnea and chest pain. Myocardial fibrosis or scarring can be detected via cardiac MRI.

Pulmonary sequelae-

The common conditions seen are dyspnea and hypoxia. Assessment of progression includes home pulse oximetry, high-resolution computed tomography of the chest and pulmonary angiogram.

Neuropsychiatric sequelae

Neuropsychiatric pathology complications are diverse in includes brain fog, depression, anxiety, PTSD, immune dysregulation, inflammation, microvascular thrombosis and iatrogenic effects of medications

Hematologic sequelae

Period of the hyper inflammatory state induced by infection with SARS-CoV-2 is not known. Thromboembolic event have been observed in less than 5% of the recovered patients.

Endocrine sequelae

It can newly affect or worsen the existing bone demineralization, subacute thyroiditis, and diabetes mellitus. Newly affected patients should undergo specific endocrine testing.

Renal sequelae

during acute COVID-19, resolution of AKI is seen in the majority of patients; however, reduced eGFR has been reported at 6months follow-up.

Gastrointestinal and hepatobiliary sequelae

Even if a patient is tested negative in COVID-19 swab test after infection, they can have continued viral faecal shedding. It can change the microbiome of the gut.

Dermatologic sequelae

COVID-19 can even cause hair loss as a powerful symptom.[86]

Multisystem inflammatory syndrome in children (MIS-C)

Patients younger than twenty-one and more than seven years of age with fever also show symptoms like dysfunction of

multiple organs and elevated inflammatory markers. They can also have neurological and cardiovascular complications.

1.5 Possible reasons for the evolution of SARS-CoV-2

Its morphology is represented by the characteristics of the Coronaviridae family. For example, it has six main ORF's, i.e., open reading frame and a total of 38% G+C content with 29.8 Kilobase of the viral genome. The general symptoms in patients were fever, cough, and chest X-ray and CT imaging analysis showed that 75% of 99 patients exhibited multiple mottling, and the remaining 25% of 99 patients exhibited unilateral pneumonia[21,20,22]From the genome sequence of the virus, isolated from six patients, it was observed that the nucleotide sequence of SARS-CoV-2 shows comparatively higher homology with SARS-CoV than with MERS-CoV conforming that SARS-CoV-2 might have evolved from SARS-CoV. Also, the seven of the conserved replicase domains revealed that 94.6% similarity in the sequence was seen in amino acids among SARS-CoV-2 and SARS-CoV. The shorter region of RdRp from BatCoV RaTG13(Bat coronavirus) showed high sequence similarity with 2019-nCoV[1]. Thus, many studies suggest that we confirm bats as a probable host with a 96.2% genome identical to bat coronavirus. Further phylogenetic analysis of full-length genome, RdRp gene, and receptor binding spike gene demonstrate that RatG13 is the closest relative of SARS-CoV-2. In the s-gene phylogeny, bat-SL-CoVZC45 was close to SARS-CoV-2 but knocked down in the basal site in the ORF 1b tree in the subgenus sarbecovirus, which indicates possible recombination in this virus. Although the receptor-binding domain of SARS-CoV-2 shows structural homology with SARS-CoV, it has a variation at amino acid residues level[21]. Even though all the studies point towards the new virus evolving from bat coronavirus, an intermediate host might be present between humans and bats. By the time of the spread, at December, the bat must be hibernating, and the sequence identity between these two viruses is lower than 90%[23] RNA recombination in high frequency is one of the significant results of the plastic genome promoting all the evolutionary forces in CoVs. This evolved in the adaptation of various hosts by this virus due to different genotypes. From the phylogenetic analysis, it is evident that few genes of SARSr-CoV, similar to bats, might hold higher similarity while some genes might show lower similarity with the genes of SARSr-CoV from humans/civets, which results in phylogenetic reposition within phylogenetic trees. This phenomenon is commonly seen in SARS-CoV, which clearly explains that the novel SARS-CoVs probably jumped bat to civet to humans[11]

1.6 Virus Spread in Humans - a Glance

The emergence of Covid-19 occurred in December 2019, and by August 01, 2021, it has reached 196,553,009 confirmed cases with 4,200,412 deaths (as per WHO), and the number is exponentially increasing. As per the earlier studies, it is almost proven that the virus has probably transmitted through the animal market in Wuhan, indicating animal to animal transmission and through droplets and direct contact, human to the human transmission might have been possible.[20] The city of Wuhan has 11 million inhabitants, and its airport is a hub for major airlines in China. Even after being a domestic airport, it has code sharing with many European and North American airlines.[24] As human-to-human transmission has been confirmed earlier, the dispersal of the virus across the world from China should have been through global traveling. From the data of the early outbreak of the virus in China, from January 24, 2020, we saw that the infection is increasing exponentially, and the mean primary reproductive number increased two to eight-fold. Another report from December 31, 2019, to January 26, 2020, showed the epidemic doubling from 6.4 days to 11.1 days. One of the major transmission causes could also be asymptomatic patients via handshakes and contaminated surfaces that had droplets of the infected person. It is also vital to note that to date, no mother to fetus transmission is recorded. The data given above is continuously changing as the situation is evolving, and soon this can be a much larger outbreak.[20] Most of the infectious diseases show seasonal patterns, which is a burden for health care centres worldwide. It was seen that a notable community transmission has occurred in a uniform east and west pattern. At first, the new epic entry of disease was approximately 30-50^{0}N' to Italy, South Korea, and Japan. Later it was seen that community transmission also started to happen in Iran, France, Spain, and North-western United States. The number of deaths and infected patients is significantly less in South East Asia compared to temperate regions[25]. Most of the other viruses from the Coronaviridae family-like SARS-CoV and MARS, also prefer cool and humid climates like SARS-CoV-2[26]. The virus's prevalence and emergence depend upon the virus's infectivity, and the other factors include economic activities, population mobility, and social environment[27].In Human beings, the virus first infects respiratory systems and alveolar cells in the lungs sacs. The cellular receptor for the SARS virus is AEC2. Using cellular machinery, the virus starts duplicating its genome and synthesizes its required proteins after infecting the cell to generate a new virus. A similar multiplication mechanism was seen in SARS-CoV and MARS virus. A multiplication mechanism is necessary for drug development. In the current scenario, doctors and researchers are designing drugs based on a similar infection in the past[14]. In addition, studies found that even though SARS is a respiratory disease, RNA of SARS-CoV can also be detected in the plasma of SARS patients after six days of the onset of the system, which can be detected using nested PCR assay. In addition, in lymphocytes at a higher concentration than plasma in any phase, indicating lymphocytes as a possible target for SARS-CoV in contrast, covid-19 patients can also be infectious during the incubation period[28]. Droplets from coughs and sneezes from patients may travel meters as multiphase turbulent gas clouds, which protects droplets from evaporating. It is clear why social distancing, use of appropriate personal protective equipment (PPE), ventilation, and hygiene are seen to reduce infection in the environment for efficient transmission, [29,30]. Studies have shown that most social distancing practices significantly reduce cases and deaths of new Covid-19[31]. Non-pharmaceutical interventions such as mask and distancing have proved to be very effective in controlling the virus spread [32]. Infection status across the world, some countries, and India is shown in Figures 1(a), 1(b), 2, and 3.

(A) Cumulative No. of Active Cases

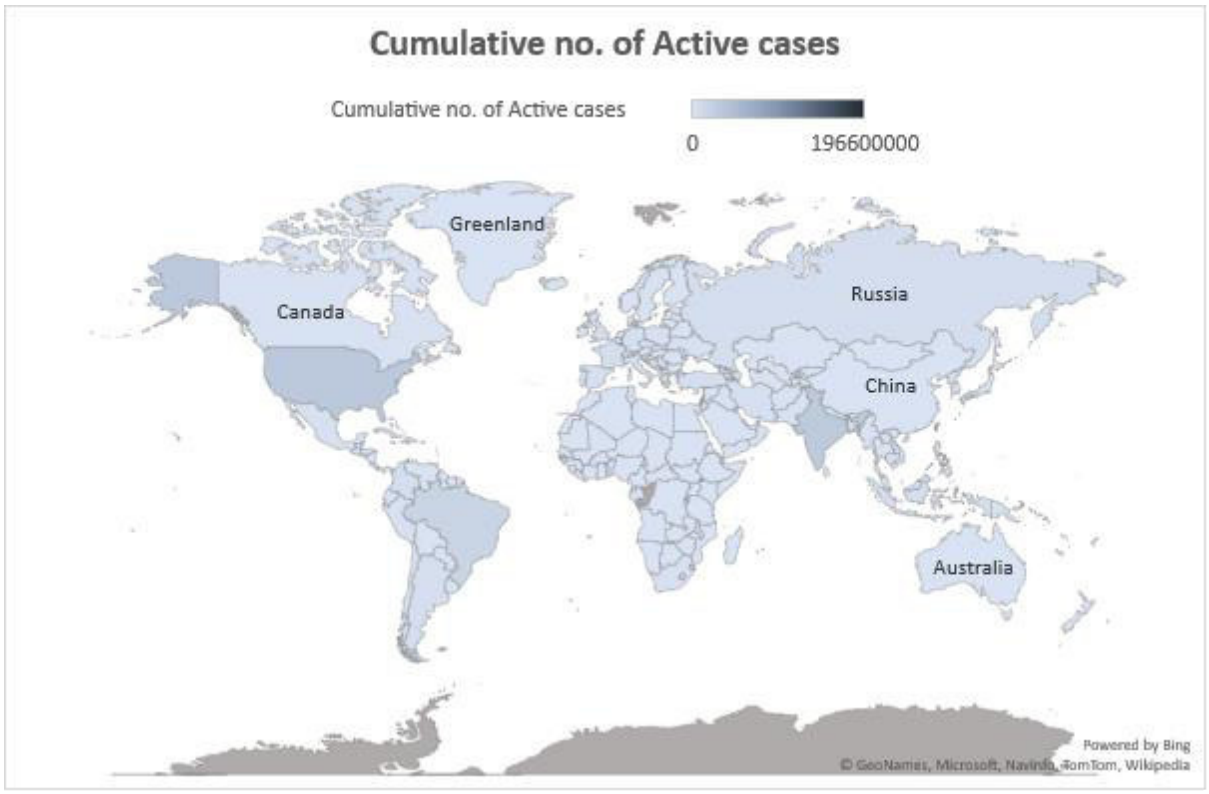


Fig 1: Covid-19 Infection Status Across World till August 01, 2021[80]

(B) Cumulative No. of Death Cases

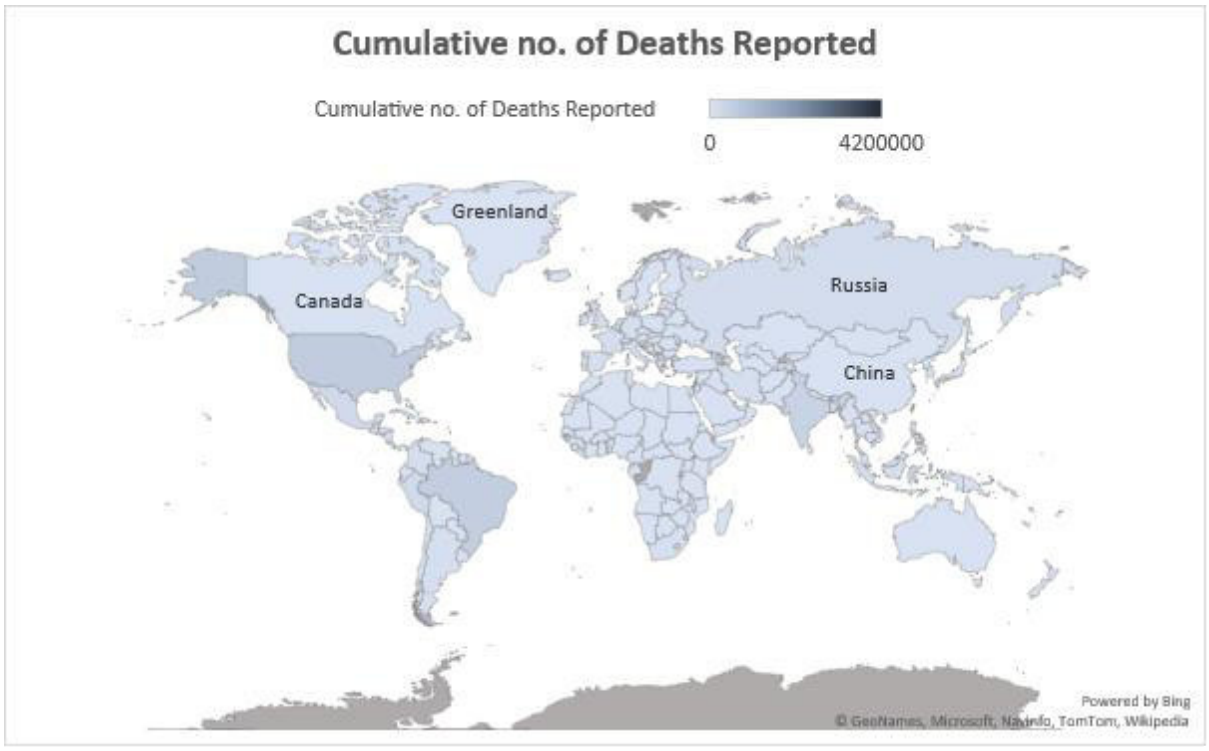


Fig 2: Covid-19 Infection Status Across Selected Counties till August 01, 2021[80]

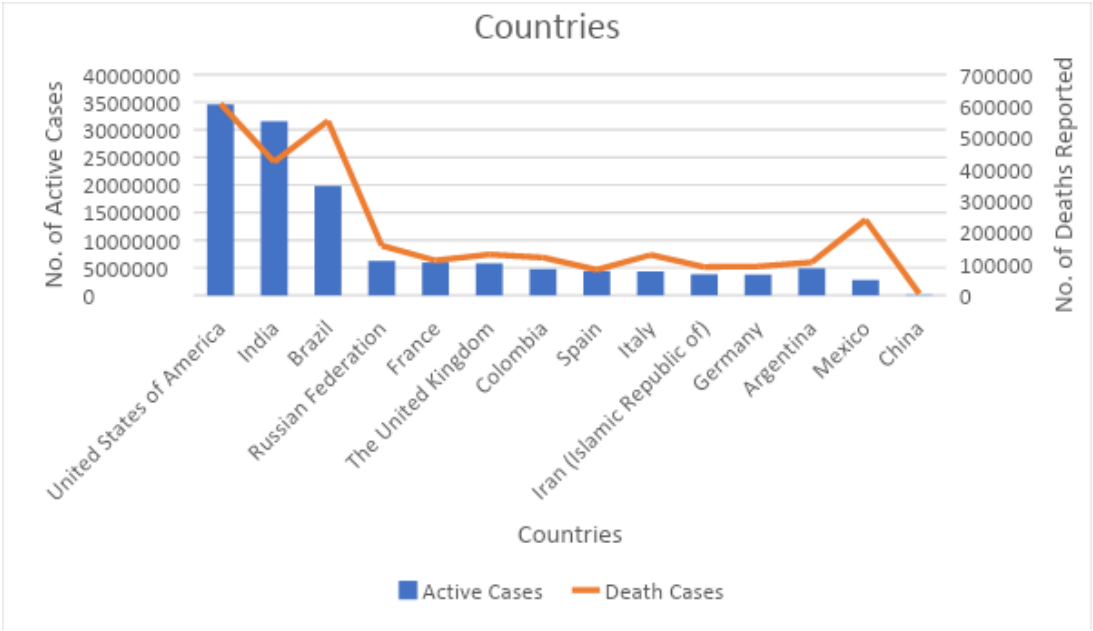
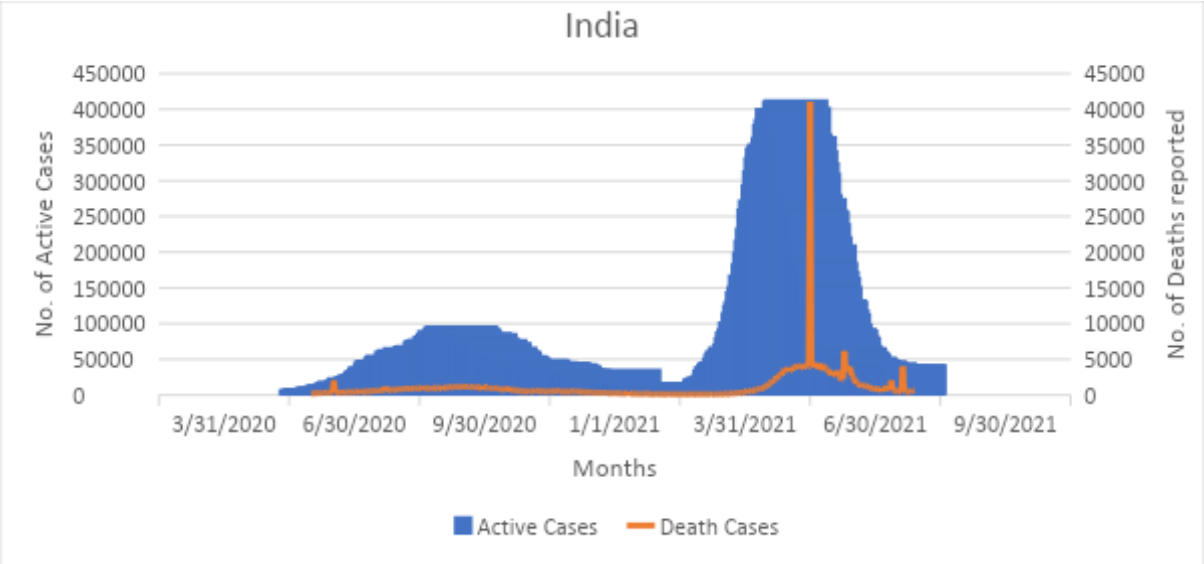


Fig 3: Covid-19 Infection Status In India till July 29, 2021[80]



1.7 Drugs Used for Treatment of Covid-19

Currently, there are some drugs approved for the treatment of COVID-19, though some of the drugs have been tried. There is a need to identify the pathology of COVID-19. Because of current needs, studies and discussions on various drug candidates against covid-19 are reviewed. SARS-CoV-2 does not have specific therapeutic agents in the medicine. Many companies and research organizations are conducting clinical trials to develop drugs against covid-19 worldwide. Drug development against covid-19 is at various stages in the world. The stages of the various drug development and drugs used to treat the covid-19 patients are reviewed as part of the review. The virally infected cases are growing every day. In India, the UK, and the USA, every day, an average of 50000 people are getting infected with covid-19. Thus, there is an instant need for an efficient treatment to treat patients having symptoms and decrease the transmission ability of the patient in the community. Thus, the social spread of the virus may be decreased. Developing a new drug is a time-consuming procedure, and now the available drug candidates are tested to treat COVID-19. The strategy of using available drug candidates minimizes the time required for a drug's safety, side effects, and drug interaction with another candidate are healthy established[33 34]. There are 15 drugs used against COVID-19[35]. The details of drugs used against COVID-19 are listed in Table 1.

Table 1: List of drugs used in the treatment of COVID-19, mechanism of action, and their current status. [36-59]

S. No.	Name of the drug	Mechanism of action if known	Current status	References
1.	Chloroquine and Hydroxychloroquine	CQ inhibits viral entry, uncoating, assembly, and the building, interfering with the glycosylation of its cellular receptor angiotensin-converting enzyme 2 receptor (ACE2). It can affect the initial stages of virus replication by inhibiting virus-endosome fusion via increasing endosomal pH.	Used to treat covid-19 patients. But clinical trials were prevented by WHO	[36,37,38,39]

2.	Azithromycin	Azithromycin prevents the virus entry into cells. Azithromycin promotes and regulates the production of type I and III interferons (especially interferon-β and interferon-λ) and the genes involved in virus recognition, such as MDA5 and RIG-I. It is more effective in combination with CQ and HCQ.	Phase-4	[40]
3.	Remdesivir	Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.	It received emergency use authorization (EUA) from the FDA on May 1, 2020,	[41]
4.	Lopinavir and Ritonavir	It inhibits 3-chymotrypsin-like protease in the human immunodeficiency virus.	It was approved during the SARS and MERS outbreak.	[42]
5.	Favipiravir	Favipiravir, otherwise known as "T-705, or Avigan," has shown a wide range of antiviral activity against many RNA viruses.	Phase 3 approved in India	[43]
6.	Tocilizumab and sarilumab	Cytokine-release syndrome is involved in exacerbating severe reactions to the virus. This causes ARDS as viral loads diminish.	Tocilizumab is under its phase 3 trial	[44,45,46,47]
7.	Umifenovir	It is a hydrophobic molecule that interacts with both proteins and lipids. It binds with the viral lipid membrane and affects the cellular trafficking of the virus.	Gained DCGI's nod for phase 4	[48]
8.	Nafamostat and Camostat	They are serine protease inhibitors. Camostat showed blocking the entry of SARS-CoV virus in vitro by acting as an antagonist to the serine protease TMPRSS2.	Phase 2/3 and Phase 2 clinical trials in Japan and the USA.	[49,50]
9.	Famotidine	The mechanism of action is still unknown for famotidine. It is believed to bind to a papain-like protease encoded by the SARS-CoV-2 genome and is believed to be essential to the entry of SARS-CoV; however, it has not been supported by any cell assay results to date.	Phase 2	[51]
10.	Nitazoxanide	It blocks the maturation of the nucleocapsid N protein of the virus that promotes the production of the viral particles.	Phase 2	[52]
11.	Ivermectin	It binds with glutamate-gated chloride ion channels in parasites, which causes depolarization of the cells. In COVID-19, it might work by binding and destabilizing cell-transport Protein, which enters the nucleus.	Phase 4	[53]
12.	Corticosteroids	These molecules inhibit the expression of genes that code for inflammatory proteins—encoding inflammatory molecules. However, they also show long-term side effects.	A variety of clinical trials are ongoing.	[54,55]
13.	Dexamethasone	Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressive effects	Phase 3	[56,57]
14.	Bevacizumab	This drug inhibits the growth of blood vessels that feed the tumor. This drug could reduce vascular permeability by suppressing VEGF, decreasing fluid entering the lungs of patients with COVID-19.	It is under phase 2 trial	[58]
15.	Fluvoxamine	Fluvoxamine is generally used to treat OCD. This selective serotonin-reuptake inhibitor binds with the sigma-1 receptor to remove the inflammatory cascade in the cells of the endoplasmic reticulum.	Phase 3.	[59]

1.8 Mutations in Covid-19

The SARS-COV-2 being an RNA virus, more likely to mutate than other viral strains. Viruses containing the genetic material RNA undergo mutations, and it may lead to highly infectious or more minor infections. Sometimes strain may even die out. While replicating, they are prone to errors because of RNA replicating enzymes resulting in the emergence of new strains. As the SARS-CoV-2 virus is also a single strand containing RNA, similar to other viruses, changing its genetic sequence this process is also known as mutation. The best example being the difference in rains from strains samples from China, Italy, and the USA. Mutations in viruses do carry potential side effects or threaten pandemics. In some cases, the mutations might also

cause a lower transmission rate or could become neutral. According to various researcher's coronavirus is undergoing mutations. Twenty-five isolates clustered together are found circulating in Thailand and multiple provinces of China [60]. The current review focuses on various mutations and their effect on the behaviour of coronavirus. The most dominant mutation of the coronavirus found common throughout European countries and was also recently discovered in Malaysia. This mutation is called D614G, and has sparked the discourse around the mutation of the coronavirus. The newly documented case of re-infection in Hong Kong, China, Italy, and the UK is also found to be affected with coronavirus that varies in their genetic structure from the virus from the first infection that the patient had caught in March this year. SARS-CoV 2 strains have been thought of similar to original strains till a novel mutation, D614G, was discovered. Even though the D614G mutation showed a higher infectious rate, humans developed little immunity against it. Mutations are not always harmful sometimes. Even the highly harmfull virus mutates to deactivate itself. Studies show, RNA viruses generally mutate into less vulnerable versions. The mutation rate of the novel coronavirus has been reported to be slow. Scientists believe a big reason might be the low immunity against infection in humans and the non-availability of vaccines. On December 14, a new variant of Covid-19 was exposed in England, the UK, which increased the cases severely[61]. This variant is referred to by WHO as SARS-CoV-2 VUI 202012/01 It is estimated that its transmissibility has been amplified by 70-80% and assumed to be a more aggressive strain than the previous ones[62]. This new strain of the virus has undergone 14 different changes, and one of them includes a mutation in N501Y, which is responsible for the virus's entrance into the human cell. Furthermore, this is the reason which amplified the transmissibility of the virus. It is also said that this variant is assumed to be more aggressive and contagious, but it is not much more dangerous than previous ones that existed in the US (i.e., D614G)[63]. The details of specific mutations are listed in Table 2 and Table 3.

Table 2. There are specific mutations that are currently of great concerns[64]

Name	Spike Protein Substitutions	First Identified	WHO labels	Attributes:
20I/501Y.V1	69del, , A570D , 70del, 144del, T716I, (E484K*), (S494P*), N501Y, , P681H, D614G, D1118H (K1191N*), S982A,	United Kingdom	Alpha	50% increases transmission, minimal impact after vaccination, no impact on EUA monoclonal antibody treatments
20H/501.V2	D80A,243del,241del,242del,K417N,D215G N501Y,D6145,E48K,A701V	South Africa	Beta	50% increases transmission, minimal impact after vaccination, considerably reduced susceptibility to the combinational monoclonal antibody treatment
21A/S:478K	T19R, D950N, (V70F*), T95I, G142D, E156-, F157-, P681R, R158G, (A222V*), L452R, (W258L*), (K417N*), T478K, D614G,	India	Delta	Increased transmissibility Potential reduction in neutralization by some EUA monoclonal antibody treatments
20J/501Y.V3	L18F, P26S, N501Y D138Y, R190S, K417T, T20N E484K, D614G, T1027I, H655Y,	Japan/Brazil	Gamma	reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment

Table 3 List of mutations in the covid-19 virus and their significance.[65-76]

Genomic position	Significance	Genomic Region	UTR/Effect on Protein	References
N501Y	It has a receptor-binding motif of the spike, this Protein, which is used by the virus, binds to the human ACE2 receptor and increases transmissibility in humans. Identified in the UK	Spike protein	N501Y/S	[65]
A23403G	Spike glycoprotein binds with the target receptor and allows membrane fusion and viral entry. This mutation leads to an amino acid substation of aspartate by glycine at 614 positions.	Spike protein	D614G/S	[66, 67]
C1059T	Threonine, uncharged polar, gets replaced by isoleucine, hydrophobic. Within protein structure, there is an interaction between threonine and hydrogen bonds with amino acids, polar. Due to this, a bend is formed because of proline and glycine relative position	Non-Structural protein 2	T85I/NSP2	[68]
C14408T	Causes an amino acid change from proline to leucine at position 323 (P323L) in RNA polymerase protein.	Non-Structural protein 12, post-	: P314L/NSP12b	[67,69]

	It is one of the most common mutations seen to date.	ribosomal frameshift (RNA-dependent RNA polymerase)		
C14805T	Many SNVs are unique clusters, but some of SNVs cross different groups. Such as C14805T, synonymous mutations exist in group B and group C, both. This covers 8 percent of worldwide samples. The majority of it also forms group C with two SNVs together.	Non-Structural protein 12, post-ribosomal frameshift (RNA-dependent RNA polymerase)	Y446Y/NSP12b	[67]
C241T	The C241T mutation alters the C-residue in the hexameric loop motif of SARS-CoV-2 SL5b. This is one of the earliest and the most prevalent (34.8%) mutations of the virus and can impact viral packaging and titers.	5' Untranslated Region	241/5'UTR	[70]
C3037T	C3037T is a synonymous mutation within the nsp3 protein95 coding gene (F924F at protein level) and may not lead to significant protein function changes.	Non-Structural protein 3 (predicted phosphoesterase)	F106F/NSP3	[71, 72]
G11083T	This mutation is more common in regions (Italy and Brazil) with higher fatality rates. It can be transmitted via RNA recombination	Non-Structural protein 6 (transmembrane protein)	L37F/NSP6	[73]
G1397A	This results in an amino acid substitution of valine by isoleucine at position 198 (V198I), and both amino acids have the same isoelectric points.	Non-Structural protein 2 encoding region of ORF1a	V198I/NSP2	[74]
G25563T	This mutation in Orf3a and N genes was dominant in the overall genetic profile exclusive to Gujarat. The find is essential as the Orf3a gene encodes a protein involved in regulating inflammation, antiviral responses, and apoptosis, said a researcher.	ORF3a protein	Q57H/ORF3a	[75]
G28881A and G28882A	Causes substitution of arginine by lysine (R203K).	Nucleocapsid protein	RG203KR/N	[71]
G28883C	Causes substitution of glycine by arginine (G204R)	Nucleocapsid protein		[71]
T26729C and C27046T	causes T175M mutation in the peptide sequence	glycoprotein coding region	A69A/M and T175M/M	[74]
T28144C	causes an L84S substitution in the ORF8 protein	ORF8 protein	L84S/ORF8	[76]
G26144T	Causes a G251V substitution in the ORF3a Protein	ORF3a protein	G251V/ORF3a	[74]

1.9 Phases of vaccine development

Development of vaccines starts from discovery, i.e., what composition of complex proteins is required for its development using transcriptomics or proteomics approach during strain generation. This is followed by the practical approach where the host-pathogen response is studied. An experimental approach on animals and in vitro studies is also made to understand the direction of the innate response. In this phase, pathogen response is recorded. For example, a natural infection sometimes causes mumps which sets benchmark for a vaccine. The Proportion of immunogenic Protein, which checks whether the composition of the Protein does not vary when produced in large amounts, is also done in this phase. The next phase includes clinical trials, which consists of 4 stages, "Clinical research" refers to studies, or trials, done in people (www.fda.gov). Where no patients or volunteers in which response is to be studied increases with each stage. After clearing all the three stages, a license is issued through authorities. Then the post-marketing study is done where the safety and efficiency of vaccines in a large population are taken care of [77]. More than 150 countries are in the race to develop a vaccine against SARS-CoV-2 as early as possible. Some are in their clinical stage (who.int), some of the leading countries and the organization have claimed to show successful results and are ready for their marketing. Below is a table for leading countries in their different clinical stages issued by WHO on July 30, 2021, under the DRAFT landscape of covid-19 candidate vaccines [78]. The details of vaccines developed by the different organizations and their status in clinical trials are listed in Table 4.

Table 4. List of vaccines developed by the different organization and their status in clinical trials.[78]

Institute/Organization	Mode of Administration	Candidate Vaccine	No. of Doses	Clinical Stage
University of Oxford, AstraZeneca (Covishield)	Intramuscular	ChAdOx1-S- (AZD1222)	1 or 2	Phase- 4
Moderna, NIAID (CX-024414)	Intramuscular	LNP-encapsulated mRNA-1273	2	Phase- 4
Sinovac Research and Development Co., Ltd (CoronaVac)	Intramuscular	Inactivated, SARS-CoV-2 Vaccine	2	Phase- 4
BioNTech, Pfizer, Fosun Pharma, Jiangsu Provincial Center for Disease Prevention and Control (Comirnaty, Tozinameran)	Intramuscular	BNT162 (3 LNP-mRNAs)	2	Phase- 4
Beijing Institute of Biological Products, Sinopharm, China national Biotec group co (BBIBP-CorV)	Intramuscular	Inactivated (Vero cell)	2	Phase- 4
CanSino Biological Inc, Beijing Institute of Biotechnology (Convidicea, Ad5-nCoV)	Intramuscular	Adenovirus Type 5 Vector	1	Phase- 4
Wuhan Institute of Biological Products, Sinopharm, China national Biotec group co	Intramuscular	Inactivated (Vero cell)	2	Phase- 3
Janssen Pharmaceutical Companies (Johnson & Johnson COVID-19 vaccine)	Intramuscular	Ad26.COV2.S	1 or 2	Phase- 3
Gamaleya Research Institute and Health Ministry of the Russian Federation (Sputnik V)	Intramuscular	Adeno-based (rAd26-S+rAd5-S)	2	Phase- 3
Novavax (NVX-CoV2373)	Intramuscular	full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M (SARS-CoV-2 rS/Matrix M1-Adjuvant)	2	Phase- 3
Anhui Zhifei Longcom Biopharmaceutical, Chinese Academy of Sciences, Institute of Microbiology. (RBD-Dimer, ZF2001)	Intramuscular	Adjuvanted Recombinant Protein (RBD-Dimer) CHO Cell	2 or 3	Phase- 3
Sichuan University and West China Hospital	Intramuscular	Sf9 Cell (baculovirus production expressed in Sf9 cells) RBD	2	Phase- 3
Curevac AG (Zorecimeran, CVnCoV)	Intramuscular	mRNA (CVnCoV Vaccine)	2	Phase- 3
Institute of Medical Biology and Chinese Academy of Medical Sciences	Intramuscular	SARS-CoV-2 vaccine, Vero cells.	2	Phase- 3
Zydus Cadila (ZyCoV-D)	Intradermal	nCov Vaccine	3	Phase- 3
Sanofi Pasteur and GSK	Intramuscular	S protein (baculovirus production)	2	Phase- 3
Beijing Minhai Biotechnology Co.	Intramuscular	Inactivated SARS- CoV-2 vaccine (Vero cell)	1,2 or 3	Phase- 3
Instituto Finlay de Vacunas	Intramuscular	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus	2	Phase- 3

		toxoid plus adjuvant)		
Academy of Military Science and Walvax Biotechnology and Suzhou Abogen Biosciences.	Intramuscular	SARS-CoV-2 mRNA Vaccine (ARCoV)	2	Phase- 3
Center for Genetic Engineering and Biotechnology (CGIB)	Intramuscular	CIGB-66 (RBD+ Aluminium hydroxide)	3	Phase- 3
Valneva, National Institute for Health Research, United Kingdom	Intramuscular	VLA2001	2	Phase- 3
Federal Budgetary Research Institute State Research Center of Virology and Biotechnology "Vector"	Intramuscular	EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19	2	Phase- 3
Bharat Biotech International Limited	Intramuscular	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	2	Phase- 3
Shenzhen Kangtai biological products co., Ltd	Intramuscular	Inactivated SARS-CoV-2 vaccine	3	Phase- 3
Nanogen Pharmaceutical Biotechnology	Intramuscular	Recombinant Sars-CoV-2 Spike protein, Aluminum adjuvanted	2	Phase- 3
Univercells, ReiThera, Leukocare	Intramuscular	Replication defective Simian Adenovirus encoding S (GRAD-COV2)	I	Phase-2/3
Inovio Pharmaceuticals, International Vaccine Institute (INO-4800)	Intradermal	DNA plasmid vaccine (INO-4800) with electroporation	2	Phase-2/3
Medicago Inc.(CoVLP)	Intramuscular	CoVLP	2	Phase-2/3
United Biomedical Inc, COVAXX	Intramuscular	Multitope peptide based S1-RBD-protein (UB-612)	2	Phase-2/3
Osaka University, AnGes, Takara Bio. (AG0301-COVID-19)	Intramuscular	Adjuvant + DNA plasmid vaccine (AG0301-COVID19)	2	Phase-2/3
ModernaTX, Inc.	Intramuscular	mRNA-1283	2	Phase-2/3
Shifa Pharmed Industrial Co	Intramuscular	COVID-19 inactivated vaccine	2	Phase-2/3
ReiThera, Univercells , Leukocare.	Intramuscular	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	I	Phase-2/3
Medigen Vaccine Biologics, NIAID, Dynavax	Intramuscular	CpG 1018+S-2p protein (MVC-COV1901)	2	Phase- 2
Clover Biopharmaceuticals Inc. GSK, Dynavax	Intramuscular	native like Trimeric subunit spike protein vaccine (CpG 1018 adjuvant + Alum adjuvant or SCB-2019 plus AS03)	2	Phase- 2
The University of Hong Kong, Beijing Wantai and Biological Pharmacy Xiamen University.	Intranasal	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu based RBD)	I	Phase- 2
Arcturus Therapeutics (Lunar-COV19/ARCT-021)	Intramuscular	mRNA (ARCT-021)	ND	Phase- 2
Erciyes University	Intramuscular	ERUCOV-VAC inactivated virus	2	Phase- 2
Razi Vaccine and Serum Research Institute	Intramuscular and Intranasal	Razi Cov Pars, recombinant spike protein	3	Phase- 2
Moderna with National Institute of Allergy and Infectious Diseases (NIAID)	Intramuscular	mRNA-1273.351. A lipid nanoparticle (LNP)-an encapsulated mRNA-based vaccine encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant.	3	Phase- 2
Guangdong Provincial Center for Disease Control and Prevention.	Intramuscular	Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	2	Phase- 2
Vaxine Pty Ltd, Medytox	Intramuscular	Recombinant spike protein with Advax adjuvant	I	Phase- 2

More than 30 organizations have successfully finished their discovery stage, and many are in their preclinical stage.[78]

1.9.1 Vaccine against Delta variant

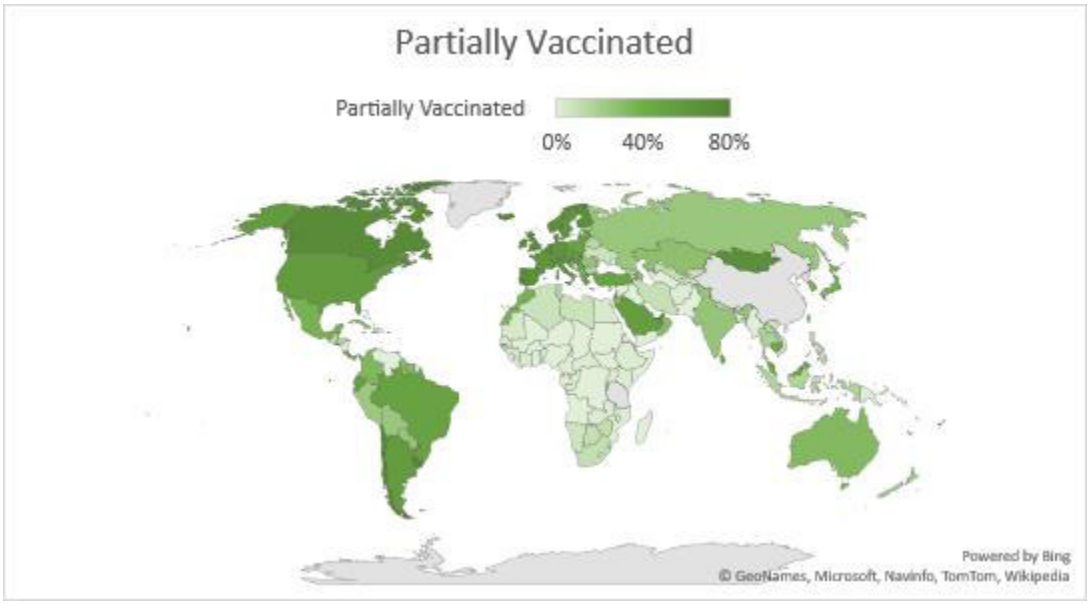
Delta variant- A spike protein mutation. Mutation in S1-S2 cleavage site is observed, which leads to an increase in its replication rate, causing higher viral load and transmission. This variant was behind India's second wave, a massive disaster in late April 2021. Vaccine effectiveness data is unclear for this variant. But few studies show that the difference is small after two doses between alpha and delta variant. This was the case for the both ChAdOx1 nCoV-19 and BNT162b2 vaccines. With BNT162b2 vaccines effectiveness was seen to be approximately 88% with two doses. And, 67% with two doses of ChAdOx1 nCoV-19 vaccine[85].

1.10 *Administration of Vaccine by different countries*

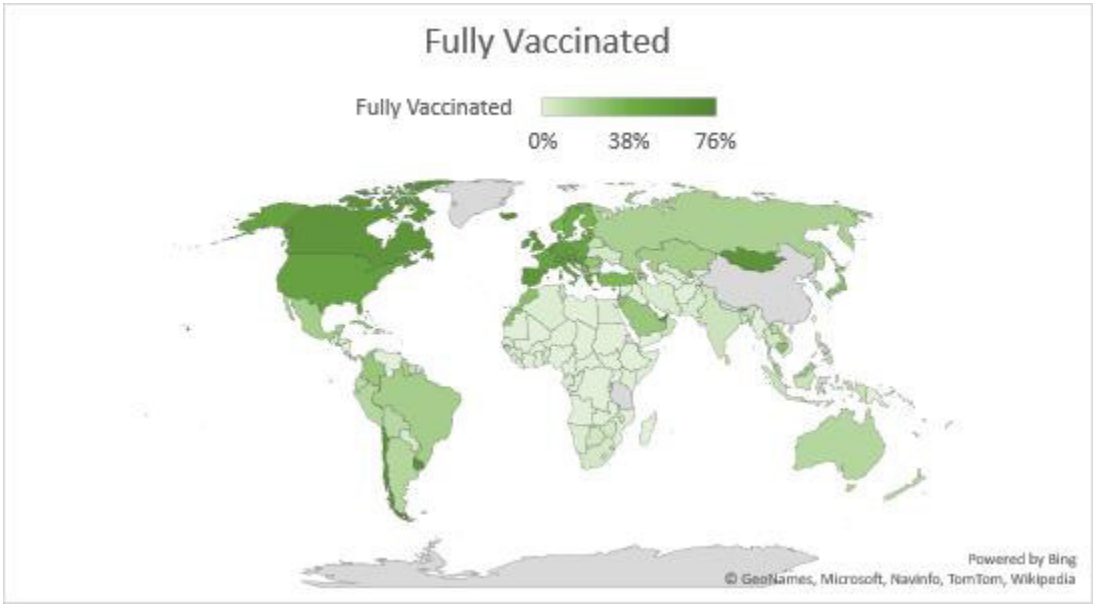
Up to August 01, 2021, more than 4.13 billion shots have been administered in the world. Every vaccine has its respective number of doses, with booster doses should be taken every year. The primarily preferred vaccine in India is Covaxin and Covishield. Both of them have two doses, and both doses should be taken in their respective time gap. Looking at all these, we can expect a solution soon and get our lives back to normal. Vaccines administered in the world are shown in Figures 4 (a) and (b).

Fig: 4 Vaccine Administered In The World till August 01, 2021[79]

(a) Partially Vaccinated Across World



(b) Fully Vaccinated Across World



Here, partially vaccinated indicates administration of at least one dose [79].

1.11 *Potential Side- Effects of the Covid-19 Vaccine*

On December 11, 2020, Emergency Use Authorization (EUA) was granted to Pfizer's mRNA vaccine, the first Covid-19 vaccine. The concern for side-effects arises soon after this news among people, and there certainly are few minor side effects of the vaccine. Still, after granting EUA, FDA passed a statement that the "vaccine has known, and potential benefits outweigh its known and potential risks. The side effects of Pfizer's vaccine involve pain, swelling, and redness at the site of the injection, fatigue, muscle and joint pain, headache, swollen lymph nodes (lymphadenopathy), low-grade fever, nausea, and chills. There is a remote probability of severe allergic reaction that the Pfizer-BioNTech COVID-19 could cause within a few minutes after getting a dose. This includes difficulty breathing, fast heartbeat, swelling of the face and throat, skin rashes, dizziness, and weakness. If any of the symptoms become severe or start to concern you immensely, then immediately consult any medical officials (fda.gov). On November 30, 2020, ModernaTX requested an Emergency Use Authorization (EUA) to FDA for the COVID-19 vaccine. The proposed dosing program is two doses, 100 µg each, administered 30 days apart. Apart from common symptoms like pain, swelling, redness at the short site, chills, headache, joint pain, fatigue, certain severe side-effects are also reported like lymphadenopathy in 173 participants in the vaccine group and 95 participants in the placebo group. There were no reported anaphylactic reactions observed in the vaccine. Three reports of facial paralysis (Bell's palsy) were also observed in the vaccine group and 1 in the placebo group. No other severe adverse effects of the vaccine-like neurologic and neuroinflammatory were observed. The most common severe adverse effect in the vaccine group includes myocardial infarction (0.03%), nephrolithiasis (0.02%) and cholecystitis (0.02%).Many vaccines were found to be effective over others. Effectiveness of vaccine produced by few top companies are- Pfizer-BioNTech vaccines is found to be 94% efficient with bearable side-effects[82]. Moderna company had assured 95% of efficacy by injecting the genome of the virus to arouse an immune response. Whereas, AstraZenca has given their efficacy in two form i.e., if both the doses are administered as per standard than it has 62% of efficacy and when first dose is halved and second dose is as per standard than it has efficiency of 90%. Bharat Biotech's Covaxin is expected to have 60% effective against this virus[83]. Russian vaccine Sputnik V is claimed to show 92% of effective rate[82]All these side effects are too little to be worried about and looking at the previous success of vaccines for polio, smallpox, etc., we should not forget how crucial these vaccines play in saving lives throughout the world. (www. fda.gov).

1.11.1 Vaccine Acceptance

There is high diversity in the acceptance rate of vaccines by society, community, or nation. The low acceptance rate is because of hesitation, delusion, and past distrust. Unacceptance can be resolved by taking the initiative to resolve their issues and understanding the importance of taking vaccines, ensuring economic and societal restoration. Organizing various campaigns will clear all misconceptions and educate them about vaccine production and its benefits. Proper communication and transparency of government will strengthen the trust in the government. This all can lead to a higher rate of vaccine approval by society[87].

2. CONCLUSION

Corona is a highly transmissible recent pandemic virus. Scientists, public and Governments need to work together in curbing COVID19 infection. COVID19 is undergoing mutations at a faster rate like England, South African and Indian strains and becoming more infectious (Delta plus strain). The best way to prevent mutation in COVID19 and emergence of new strains is to prevent the rate of spread. Research in COVID19 is essential and has a high influence on the economies and education of various countries in the world. Even though vaccination is available, further research is needed in development of drugs and their mechanisms.

3. AUTHOR CONTRIBUTION STATEMENT:

It is to declare that Rimjhim Singh contributed the introduction, evolution of SARS CoV2, Virus spread in humans at a glance, evolution of covid19 virus, stages of vaccine development, types of vaccines, potential side effects of vaccines and status of vaccination. Neha Bothra contributed data analysis. Origin of SARV CoV, Phylogeny, symptoms, and morphological characters of covid19. Dr. Murali Mohan Challa contributed an abstract of the review, types of drugs used to treat covid19 infection, mutations observed in covid19 virus and conclusions. Dr. Prameela Kandra contributed proof reading and English corrections

4. ACKNOWLEDGMENT

Rimjhim Singh, Neha Bothra, Murali Mohan Challa and Prameela Kandra are thankful to the Head, Department of Biotechnology, and the GITAM (Deemed to be) University Management for their support and encouragement in research.

5. CONFLICT OF INTEREST

Conflict of interest declared of none

6. REFERENCES

1. Summary of probable SARS cases with onset of illness from November 01 2002 to July 31 2003; Published October 15, 2003. Available from: http://www.who.int/csr/sars/country/table2003_09_23/en/.
2. Acute respiratory syndrome in China; Published October 15, 2003. Available from: http://www.who.int/csr/don/2003_2_20/en/.
3. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, Laman JD, de Jong T, van Doornum G, Lim W, Ling AE, Chan PK, Tam JS, Zambon MC, Gopal R, Drosten C, van der Werf S, Escriou N, Manuguerra JC, Stöhr K, Peiris JS, Osterhaus AD. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet. 2003;362(9380):263-70. doi: 10.1016/S0140-6736(03)13967-0, PMID 12892955.
4. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, Tellier R, Draker R, Adachi D, Ayers M, Chan AK, Skowronski DM, Salit I, Simor AE, Slutsky AS, Doyle PW, Krajden M, Petric M, Brunham RC, McGeer AJ, National Microbiology Laboratory, Canada, Canadian Severe Acute Respiratory Syndrome Study Team. Identification of severe acute respiratory syndrome in Canada. N Engl J Med. 2003;348(20):1995-2005. doi: 10.1056/NEJMoa030634, PMID 12671061.
5. Gibbs AJ, Gibbs MJ, Armstrong JS. The phylogeny of SARS coronavirus. Arch Virol. 2004;149(3):621-4. doi: 10.1007/s00705-003-0244-0, PMID 14991447.
6. Robertson MP, Igel H, Baertsch R, Haussler D, Ares M, Scott WG. The structure of a rigorously conserved RNA element within the SARS virus genome. PLOS Biol. 2005;3(1):e5. doi: 10.1371/journal.pbio.0030005, PMID 15630477.
7. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536-44. doi: 10.1038/s41564-020-0695-z, PMID 32123347.
8. Jaimes JA, André NM, Chappie JS, Millet JK, Whittaker GR. Phylogenetic analysis and structural modeling of SARS-CoV-2 spike protein reveals an evolutionary distinct and proteolytically sensitive activation loop. J Mol Biol. 2020;432(10):3309-25. doi: 10.1016/j.jmb.2020.04.009, PMID 32320687.
9. Alfaraj SH, Al-Tawfiq JA, Alzahrani NA, Altwaijri TA, Memish ZA. The impact of co-infection of influenza A virus on the severity of Middle East Respiratory Syndrome coronavirus. J Infect. 2017;74(5):521-3. doi: 10.1016/j.jinf.2017.02.001, PMID 28189714.
10. Yip CW, Hon CC, Shi M, Lam TT, Chow KY, Zeng F, Leung FC. Phylogenetic perspectives on the epidemiology and origins of SARS and SARS-like coronaviruses. Infect Genet Evol. 2009;9(6):1185-96. doi: 10.1016/j.meegid.2009.09.015, PMID 19800030.
11. Luk HKH, Li X, Fung J, Lau SKP, Woo PCY. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. Infect Genet Evol. 2019;71:21-30. doi: 10.1016/j.meegid.2019.03.001, PMID 30844511.
12. Groneberg DA, Hilgenfeld R, Zabel P. Molecular mechanisms of severe acute respiratory syndrome (SARS). Respir Res. 2005;6(1):8. doi: 10.1186/1465-9921-6-8, PMID 15661082.
13. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, Chen H, Wang D, Liu N, Liu D, Chen G, Zhang Y, Li D, Li J, Lian H, Niu S, Zhang L, Zhang J. Characteristics of COVID-19 infection in Beijing. J Infect. 2020;80(4):401-6. doi: 10.1016/j.jinf.2020.02.018, PMID 32112886.
14. S. chikkara bhupender, Rathi B, Singh J. Corona virus SARS-CoV-2 disease COVID-19: infection, prevention and clinical advances of the prospective chemical drug therapeutics.
15. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26(4):450-2. doi: 10.1038/s41591-020-0820-9, PMID 32284615.
16. Woo PCY, Lau SKP, Huang Y, Yuen KY. Coronavirus diversity, phylogeny and interspecies jumping. Exp Biol Med (Maywood). 2009;234(10):1117-27. doi: 10.3181/0903-MR-94, PMID 19546349.
17. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, Dhama K, Yatoo MI, Bonilla-Aldana DK, Rodriguez-Morales AJ. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med. 2020;28(2):174-84. PMID 32275259.
18. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;4(6):1011-33. doi: 10.3390/v4061011, PMID 22816037.
19. Fowler VL, Armson B, Gonzales JL, Wise EL, Howson ELA, Vincent-Mistiaen Z, Fouch S, Maltby CJ, Grippon S, Munro S, Jones L, Holmes T, Tillyer C, Elwell J, Sowood A, de Peyer O, Dixon S, Hatcher T, Patrick H, Laxman S, Walsh C, Andreou M, Morant N, Clark D, Moore N, Houghton R, Cortes NJ, Kidd SP. A highly effective reverse-transcription loop-mediated isothermal amplification (RT-LAMP) assay for the rapid detection of SARS-CoV-2 infection. J Infect. 2021;82(1):117-25. doi: 10.1016/j.jinf.2020.10.039, PMID 33271166.
20. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924.
21. Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci. 2020;16(10):1678-85. doi: 10.7150/ijbs.45053, PMID 32226285.
22. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. doi: 10.1038/s41586-020-2012-7, PMID 32015507.
23. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, Butt KM, Wong KL, Chan KW, Lim W, Shortridge KF, Yuen KY, Peiris JS, Poon LL. Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China. Science. 2003;302(5643):276-8. doi: 10.1126/science.1087139, PMID 12958366.

24. Biscayart C, Angeleri P, Lloveras S, do Chaves T. SS, Schlagenhauf P, Rodríguez-Morales AJ. The next big threat to global health? 2019 novel coronavirus): What advice can we give to travellers? – Interim recommendations. Travel Med Infect Dis (2019-. January 2020, from the Latin-American society for Travel Medicine (SLAMVI);33 2020:101567. doi: 10.1016/j.tmaid.2020.101567.
25. Sajadi MM, Habibzadeh P, Vintzileos A, Shokouhi S, Miralles-Wilhelm F, Amoroso A. Temperature and latitude analysis to predict potential spread and seasonality for COVID-19. SSRN electron. J Publ Online. 2020. doi: 10.2139/ssrn.3550308.
26. Gupta S, Raghuwanshi GS, Chanda A. Effect of weather on COVID-19 spread in the US: A prediction model for India in 2020. Sci Total Environ. 2020;728:138860. doi: 10.1016/j.scitotenv.2020.138860.
27. Zhao Z, Li X, Liu F, Zhu G, Ma C, Wang L. Prediction of the COVID-19 spread in African countries and implications for prevention and control: A case study in South Africa, Egypt, Algeria, Nigeria, Senegal and Kenya. Sci Total Environ. 2020;729:138959. doi: 10.1016/j.scitotenv.2020.138959.
28. Chang L, Yan Y, Wang L. Coronavirus Disease 2019: coronaviruses and blood safety. Transfus Med Rev. 2020;34(2):75-80. doi: 10.1016/j.tmrv.2020.02.003, PMID 32107119.
29. Majra D, Benson J, Pitts J, Stebbing J. SARS-CoV-2 (COVID-19) superspreader events. J Infect. 2021;82(1):36-40. doi: 10.1016/j.jinf.2020.11.021, PMID 33245943.
30. Cheng VC-C, Wong SC, Chuang VW-M, So SY, Chen JH, Sridhar S, To KK, Chan JF, Hung IF, Ho PL, Yuen KY. The role of community-wide wearing of face mask for control of coronavirus disease 2019 (COVID-19) epidemic due to SARS-CoV-2. J Infect. 2020;81(1):107-14. doi: 10.1016/j.jinf.2020.04.024, PMID 32335167.
31. Piovani D, Christodoulou MN, Hadjidemetriou A, Pantavou K, Zaza P, Bagos PG, Bonovas S, Nikolopoulos GK. Effect of early application of social distancing interventions on COVID-19 mortality over the first pandemic wave: an analysis of longitudinal data from 37 countries. J Infect. 2021;82(1):133-42. doi: 10.1016/j.jinf.2020.11.033, PMID 33275956.
32. Fricke LM, Glöckner S, Dreier M, Lange B. Impact of non-pharmaceutical interventions targeted at COVID-19 pandemic on influenza burden—a systematic review. J Infect. 2021;82(1):1-35. doi: 10.1016/j.jinf.2020.11.039, PMID 33278399.
33. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents. 2020;55(3):105923. doi: 10.1016/j.ijantimicag.2020.105923.
34. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-Int J Antimicrob Agents. 2020;55(4):105932. doi: 10.1016/j.ijantimicag.2020.105932.
35. Shaffer L. 15 Drugs being tested to treat COVID-19 and how they would work. Nat Med. 2020:d41591-020-00019-9. doi: 10.1038/d41591-020-00019-9, PMID 32415251.
36. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.
37. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr. 2020;14(3):241-6. doi: 10.1016/j.dsx.2020.03.011, PMID 32247211.
38. Schaper C. A mechanism of action for hydroxychloroquine and azithromycin to inhibit coronavirus disease COVID-19; 2020. doi: 10.26434/chemrxiv.12148914.v1.
39. Hashem AM, Alghamdi BS, Algaissi AA, Alshehri FS, Bukhari A, Alfaleh MA, Memish ZA. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. Travel Med Infect Dis. 2020;35:101735. doi: 10.1016/j.tmaid.2020.101735.
40. Bleyzac N, Goutelle S, Bourguignon L, Tod M. Azithromycin for COVID-19: more than just an antimicrobial? Clin Drug Investig. 2020;40(8):683-6. doi: 10.1007/s40261-020-00933-3, PMID 32533455.
41. Remdesivir EUA letter of authorization. Available from: https://www.fda.gov/media/137564/download.
42. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787-99. doi: 10.1056/NEJMoa2001282, PMID 32187464.
43. Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, Kozaki K, Nomura N, Egawa H, Minami S, Watanabe Y, Narita H, Shiraki K. In vitro and in vivo activities of anti-influenza virus Compound T-705. Antimicrob Agents Chemother. 2002;46(4):977-81. doi: 10.1128/AAC.46.4.977-981.2002, PMID 11897578.
44. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3, PMID 32171076.
45. Tocilizumab in COVID-19 pneumonia (TOCIVID-19) (TOCIVID-19). Available from: https://clinicaltrials.gov/ct2/show/NCT04317092.
46. Sarilumab COVID-19. Available from: https://clinicaltrials.gov/ct2/show/NCT04327388.
47. Park B, D pharm. US Trial Investigating Sarilumab for COVID-19 Stopped. Available from: Jul 7, 2020 https://www.empr.com/home/news/drugs-in-the-

pipeline/sarilumab-interleukin-6-antagonist-covid19-mechanical-ventilation/.
48. Umifenovir in hospitalized COVID-19 patients (UAIIC). Available from: https://clinicaltrials.gov/ct2/show/NCT04350684.
49. Clinical efficacy of nafamostat mesylate for COVID-19 pneumonia. Available from: https://clinicaltrials.gov/ct2/show/NCT04350684.
50. The impact of camostat mesilate on COVID-19 infection (CamoCO-19). Available from: https://clinicaltrials.gov/ct2/show/NCT04321096. Vol. 66.
51. Famotidine outpatient COVID-19 treatment [study.67]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04389567.
52. Hydroxychloroquine vs nitazoxanide in patients with COVID-19. Available from: https://clinicaltrials.gov/ct2/show/NCT04341493.
53. COVidIVERmectin: ivermectin for treatment of Covid-19 (COVER). Available from: https://clinicaltrials.gov/ct2/show/NCT04438850.
54. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care. 2019;23(1):99. doi: 10.1186/s13054-019-2395-8, PMID 30917856.
55. Kunz N. A trial of chronotherapy of corticosteroids in duchenne muscular Dystrophy.71. Available from: https://clinicaltrials.gov/ct2/show/NCT02036463.
56. Coronavirus disease (COVID-19): dexamethasone. Published online June 25, 2020. 72. Available from: https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-dexamethasone.
57. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704. doi: 10.1056/NEJMoa2021436, PMID 32678530.
58. Bevacizumab in severe or critical patients with COVID-19. Pneumonia (BEST-CP);75.
59. Rosen DA, Seki SM, Fernández-Castañeda A, Beiter RM, Eccles JD, Woodfolk JA, Gaultier A. Modulation of the sigma-1 receptor–IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019;11(478):eaau5266. doi: 10.1126/scitranslmed.aau5266, PMID 30728287.
60. Zhang J, Ma K, Li H, Liao M, Qi W. The continuous evolution and dissemination of 2019 novel human coronavirus. J Infect. 2020;80(6):671-93. doi: 10.1016/j.jinf.2020.02.001, PMID 32092385.
61. hart robert. A new variant of covid-19 has emerged in england- here is what it could mean for the pandemic and vaccines.33. Available from: https://www.forbes.com/sites/roberthart/2020/12/15/a-new-strain-of-covid-19-has-emerged-in-englandhere-is-what-it-could-mean-for-the-pandemic-and-vaccines/?sh=7046fd9570f6.
62. COVID-19 Update: new mutated coronavirus strain is a" super-spreader" with 70% increased transmissibility, says Centre. Available from: https://www.freepressjournal.in/india/covid-19-update-new-mutated-coronavirus-strain-is-a-super-spreader-with-70-increased-transmissibility-says-centre. Vol. 34; Published December 22, 2020.
63. Here's what we know about the U.K. coronavirus variant. Available from: https://www.washingtonpost.com/health/2020/12/20/new-covid-mutation-uk/. Vol. 32.
64. SARS-CoV-2 variant classifications and definitions; Published July 27, 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html.
65. Mutation. Published December 22, 2020;N501Y — threats, myths and reality of UK's new coronavirus strain:77.
66. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020;11(1):1620. doi: 10.1038/s41467-020-15562-9, PMID 32221306.
67. Liu S, Shen J, Fang S, Li K, Liu J, Yang L, Hu CD, Wan J. Genetic spectrum and distinct evolution patterns of SARS-CoV-2. Front Microbiol. 2020;11:593548. doi: 10.3389/fmicb.2020.593548.
68. Gaurav S, Pandey S, Puvar A, et al. Identification of unique mutations in SARS-CoV-2 strains isolated from India suggests its attenuated pathotype. Microbiology. 2020. doi: 10.1101/2020.06.06.137604.
69. Pachetti M, Marini B, Benedetti F, Giudici F, Mauro E, Storici P, Masciovecchio C, Angeletti S, Ciccozzi M, Gallo RC, Zella D, Ippodrino R. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. J Transl Med. 2020;18(1):179. doi: 10.1186/s12967-020-02344-6, PMID 32321524.
70. Mishra A, Pandey AK, Gupta P, et al. Mutation landscape of SARS-CoV-2 reveals five mutually exclusive clusters of leading and trailing single nucleotide substitutions. Genomics. 2020. doi: 10.1101/2020.05.07.082768.
71. Eskier D, Karakülah G, Suner A, Oktay Y. RdRp mutations are associated with SARS-CoV-2 genome evolution. PeerJ. 2020;8:e9587. doi: 10.7717/peerj.9587, PMID 32742818.
72. Hudson B S, Kolte V, Khan A, Sharma G. Dynamic tracking of variant frequencies depicts the evolution of mutation sites amongst SARS-CoV-2 genomes from India. J Med Virol. 2021;93(4):2534-7. doi: 10.1002/jmv.26756, PMID 33368386.
73. Benvenuto D, Angeletti S, Giovanetti M, Bianchi M, Pascarella S, Cauda R, Ciccozzi M, Cassone A. Evolutionary analysis of SARS-CoV-2: how mutation of Non-Structural Protein 6 (NSP6) could affect viral autophagy. J Infect. 2020;81(1):e24-7. doi: 10.1016/j.jinf.2020.03.058, PMID 32283146.
74. Mercatelli D, Giorgi FM. Geographic and genomic distribution of SARS-CoV-2 mutations. Front Microbiol. 2020;11:1800. doi: 10.3389/fmicb.2020.01800, PMID 32793182.
75. Joshi M, Puvar A, Kumar D, et al. Genomic variations in SARS-CoV-2 genomes from Gujarat: underlying role of variants in disease epidemiology. Genomics. 2020. doi: 10.1101/2020.07.10.197095.
76. Badua CLDC, Baldo KAT, Medina PMB. Genomic and proteomic mutation landscapes of SARS-CoV-2. J Med

Virol. 2021;93(3):1702-21. doi: 10.1002/jmv.26548, PMID 32970329.
77. Raeven RHM, van Riet E, Meiring HD, Metz B, Kersten GFA. Systems vaccinology and big data in the vaccine development chain. Immunology. 2019;156(1):33-46. doi: 10.1111/imm.13012, PMID 30317555.
78. DRAFT landscape of COVID-19 candidate vaccines; Published February 12, 2021. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
79. Holder J. Tracking coronavirus vaccinations around the world. Available from: https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html. Vol. 94; Published August 2, 2021.
80. COVID-19 coronavirus pandemic [internet]; 2021. Available from: https://www.worldometers.info/coronavirus/.
81. Julia Ries. Researchers ID 6 COVID-19 Symptom Sets: How That Will Help High-Risk Patients. 2020 Jul 31; Available from: https://www.healthline.com/health-news/researchers-id-6-covid-19-symptom-sets-how-that-will-help-high-risk-patients
82. Explained: How effective are the top vaccines for Covid-19, and when will they be available? Available from: https://indianexpress.com/article/explained/covid-vaccines-effectiveness-pfizer-moderna-oxford-when-will-they-be-available-7https://indianexpress.com/article/explained/covid-vaccines-effectiveness-pfizer-moderna-oxford-when-will-they-be-available-7058464/058464/
83. Coronavirus vaccine: List of top candidates, storage, price; all you need to know. Available from: https://www.businesstoday.in/industry/pharma/story/coronavirus-vaccine-list-of-top-candidates-storage-price-all-you-need-to-know-280107-2020-11-30
84. Redhwan Ahmed A-N, Lutfi A, Salem M, Al-Rashidi R, Hisham A. Epidemiology of Covid-19 in Yemen: A Descriptive Study. Int J Pharma Bio Sci [Internet]. 2020 Dec 28 [cited 2021 Nov 13];10(5). Available from: https://www.ijlpr.com/abstract1.php?aid=658
85. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021 Aug 12;385(7):585–94.
86. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601–15
87. Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med. 2021 Feb;27(2):225–8.
88. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N. Post-acute COVID-19 syndrome. Nature medicine. 2021 Apr;27(4):601-15.