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Review Article

A BRIEF DESCRIPTION OF COVID-19 PULMONARY VIRAL INFECTION AND REPURPOSING OF DRUGS FOR ITS TREATMENT

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ABSTRACT

A novel coronavirus disease, which is transmitted from human to human has quickly become the cause of the current worldwide health crisis. This virus is, also known as SARS coronavirus, belongs to the *Coronaviridae* family of viruses. The recent outbreak of acute respiratory disorders starting in Wuhan, China is found to be caused by this virus. The condition caused by it, known as COVID-19 has spread very rapidly all over the world, causing so many death. This led WHO on Mar 11, 2020, to designate it as a global pandemic. An update on the history, etiology, epidemiology, pathophysiology and preventive methods for COVID-19 such as masking, quarantine, and social distancing are discussed in this paper. Repurposed drugs, antibodies, corticosteroids, vaccination and plasma transfusion, are among the treatments explained in the study. Finally, the study discusses India's COVID vaccination programme. The major aspects of this entire review are to describe COVID-19 infection, its prevention and treatment approach.

Keywords: COVID-19, Repurposed drug, Convalescent plasma therapy, Antiviral drug, Plasma therapy, Vaccination

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 causes one of the most lethal and contagious viral disorder of all time, Novel Coronavirus Disease (COVID-19), which shows some severe tragic effects that leads to about 6 million deaths all over the world. It originated in Wuhan city in China in the month of December 2019, but in a short period, it rapidly spread to all other countries in the world. COVID-19 was designated as a global pandemic by the World Health Organisation (WHO) in March 2020 [1]. The transmission of the novel coronavirus occurs from one person to another when they breathe in the contaminated air containing the virus when they are in the vicinity of an infected person. Various COVID-19 diagnosis testing methods are also developed like real-time reverse transcription-polymerase chain reaction (rRT-PCR), reverse transcription loop-mediated isothermal amplification (RT-LAMP) and transcription-mediated amplification (TMA) through which virus nucleic acid detection occurs [2].

The SARS CoV-2 genetic sequencing report was firstly published on January 11, 2020. Based on that report, researchers of the global RandD department developed vaccines against the disease [3]. In the treatment of COVID-19 illness, various antiviral drugs are used as repurposed along with monoclonal antibodies and anti-inflammatory and immunomodulatory agents [4].

We searched the studies in three databases, including Google Scholar, PubMed, and Elsevier websites, for the last ten years to find all related articles on Covid-19. Papers with any language having an English abstract were included in the first step of the search. We used the following words and terms, including: "COVID-19", "coronavirus", "repurposed drug", and "vaccination". Inclusion criteria in the present study were the studies assessing the epidemiology, etiology, pathophysiology, preventive, and treatment of Covid-19, but the papers with insufficient data, the abstract without full text, in conformity between methods and results, the inappropriate explanation of the findings were excluded from this review.

History

Novel SARS CoV-2 virus first starts to spread from Wuhan city, China and was marked as a pandemic all around the globe by WHO on 11th March 2020 [5]. COVID-19 after its declaration as a global pandemic, have been overwhelmed many healthcare systems worldwide. COVID-19 pandemic shows loss of livelihood due to persistent lockdown and also shows an effect on the global economy. SARS CoV-2 have been causing worldwide chaos continuing with the second and third wave of the outbreak of this disease due to the mutant variants of the virus [6]. In Italy first confirmed case was in January 2020 of tourists coming from China and the maximum number of death was seen in March 2020. After that United States reported more death cases than China and Italy in March 2020 [7].

But before SARS CoV-2 viral infection, severe acute respiratory syndrome (SARS) was caused by SARS-related coronavirus and it was a very fatal viral respiratory disease, firstly identified in the month of February 2003 in China and spread 4 more European and Asian countries. SARS was the first fatal and rapidly transmissible disease in the 21st century. In SARS infection, most cases were in the age group of 25-70 y old, and few suspects have been reported among children under the age group of 15 y. According to the WHO report of 2003 probable and suspected cases were around 3% and the fatality rate was 9.3% [8, 9].

Etiology

Coronavirus contains encapsulated, single-stranded ribonucleic acid with surface spike protein that varies from 9-12 nm in length [10]. The viral entry into the host cell is caused by the binding of the spike protein to the ACE-2 (Angiotensin-converting enzyme-2) receptor that leads to the subsequent fusion of the virus' envelope and cell membranes of the host [11]. The new coronavirus was discovered to be phylogenetically more related to bat-derived coronavirus strains (88 percent similarity) than to human-infecting coronaviruses such as SARS (79 percent similarity) and MERS (88 percent similarity) (50 percent similarity) [12]. SARS CoV-2 are most progeny due to their mutation ability or they are most prone against human host due to their genetic evolution. SARS Coronavirus is a positive-stranded RNA virus (+ssRNA) which shows a crown-like appearance under the electron microscope. Viruses also contain envelop and spike glycoprotein on the surface of the envelope. SARS CoV-2 have great ability against mutation due to their nature of susceptible to genetic development. Several variants of SARS CoV-2 were reported by WHO in December 2021 almost five variants like Alpha, Beta, Gamma, Delta, and Omicron and according to the recent update of

2022 from France, Deltacron are a new hybrid variant of Delta and Omicron has been identified [13, 14].

Some variants of the coronavirus-2 are listed below:

B.1.1.7 (Alpha): earliest documented sample firstly in the UK in Sept 2020.

B.1.351 (Beta): earliest documented sample in South Africa on May 2020.

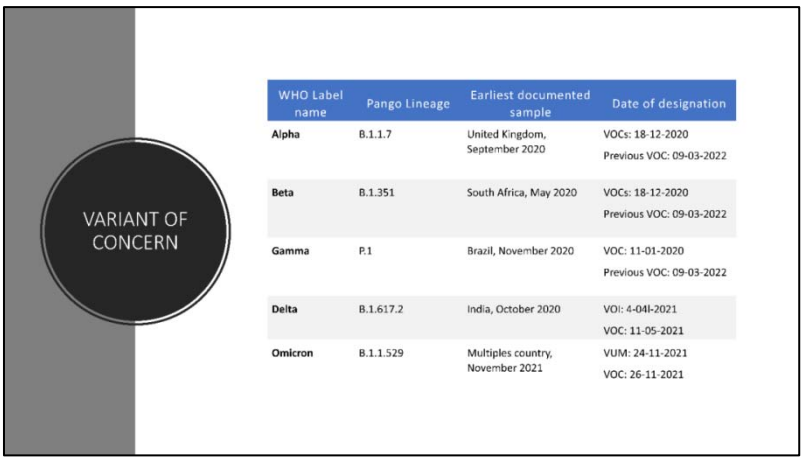
P.1 (Gamma): firstly, the sample was documented in Brazil in Nov 2020.

B.1.617.2 (Delta): First documented sample was observed in India in Oct 2020.

B.1.1.529 (Omicron): Variant documented in multiple countries in Nov 2021.

XE (Delta+Omicron combined new hybrid variant): Firstly, documented sample in France in Jan 2022 [15].

Fig. (fig. 1, fig. 2, fig. 3) show the different types of variants of coronavirus found after its spread [16].

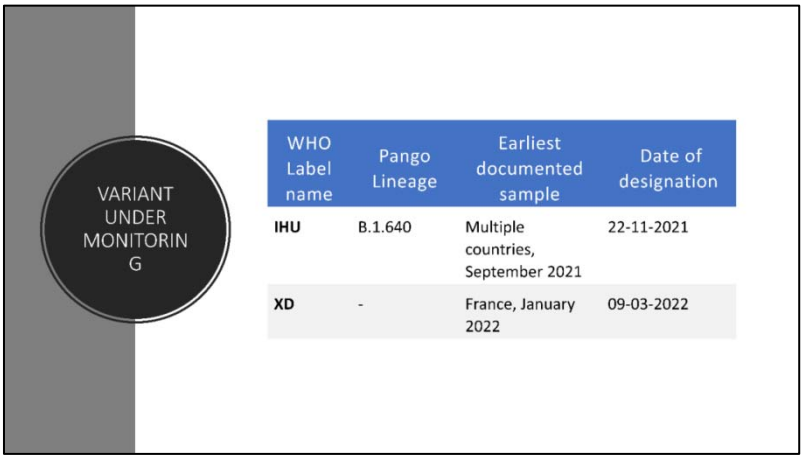


WHO Label name	Pango Lineage	Earliest documented sample	Date of designation
Alpha	B.1.1.7	United Kingdom, September 2020	VOCs: 18-12-2020 Previous VOC: 09-03-2022
Beta	B.1.351	South Africa, May 2020	VOCs: 18-12-2020 Previous VOC: 09-03-2022
Gamma	P.1	Brazil, November 2020	VOC: 11-01-2020 Previous VOC: 09-03-2022
Delta	B.1.617.2	India, October 2020	VOI: 4-04l-2021 VOC: 11-05-2021
Omicron	B.1.1.529	Multiples country, November 2021	VUM: 24-11-2021 VOC: 26-11-2021

Fig. 1: Variant of concern of CoV-2 [16] (McIntosh *et al. 2022*)

WHO Label name	Pango Lineage	Earliest documented sample	Date of designation
Epsilon	B.1.427 B.1.429	United States of America, March 2020	VOI: 05-03-2021 Previous VOI: 06-07-2021
Zeta	P2	Brazil, April 2020	VOI: 17-03-2021 Previous VOI: 06-07-2021
Eta	B.1.525	Multiple country, December 2020	VOI: 17-03-2021 Previous VOI: 20-09-2021
Theta	P3	Philippines, January 2021	VOI: 24-03-2021 Previous VOI: 06-07-2021
Iota	B.1.526	United States of America, November 2020	VOI: 24-03-2021 Previous VOI: 20-09-2021
Kappa	B.1.617.1	India, October 2020	VOI: 04-04-2021 Previous VOI: 20-09-2021
Lambda	C.37	Peru, December 2020	VOI: 14-06-2021 Previous VOI: 09-03-2022
Mu	B.1.621	Colombia, January 2021	VOI: 30-08-2021 Previous VOI:09-03-2022

Fig. 2: Variant of interest of CoV-2 [16] (McIntosh *et al. 2022*)



WHO Label name	Pango Lineage	Earliest documented sample	Date of designation
IHU	B.1.640	Multiple countries, September 2021	22-11-2021
XD	-	France, January 2022	09-03-2022

Fig. 3: Variant under the monitoring of CoV-2 [16] (McIntosh *et al. 2022*)

Epidemiology update on covid-19 up to April 2022

Since the first occurrences of COVID-19 were recorded in the city of Wuhan in Hubei Province, China, this highly transmissible infectious disorder has made its way rapidly to about 223 nations, resulting in above 281 million cases and 5.4 million fatalities. According to a recent WHO epidemiological update, the SARS-Coronavirus-2 variants of concern have been detected in more than 200 countries throughout the world, with the newest variants of concern (VOC), Omicron, being reported by 76 countries so far subsequently happened at the beginning of November 2021 [17]. On January 30, 2020, the first verified case in India was discovered in Thrissur, Kerala. On March 5, 2020, the first infected individual in Uttar Pradesh (UP) was discovered in Ghaziabad. The fig. (fig. 4) shows the epidemiological description of COVID-19 [18].

SARS Coronavirus-2 infection is a severe sickness that can affect people of all ages. Severe COVID infection is more likely to develop in old people (>60 y) and the person dealing with some medical comorbidities, including cardiovascular disease, renal disease, obesity, diabetes, chronic pulmonary disease, cancer, etc. According to an investigation done on the confirmed cases reported to the Chinese Centre for Disease Control (CDC) from Jan 22 to May 30, 2020, the percentage of COVID-19 patients requiring hospitalization was 6 folds greater in individuals with prior health issues (45.4 % vs. 7.6 %) [19].

According to the WHO global report up to 24 April 2022, over 500 million confirmed cases and 6 million total deaths have been recounted worldwide [20].

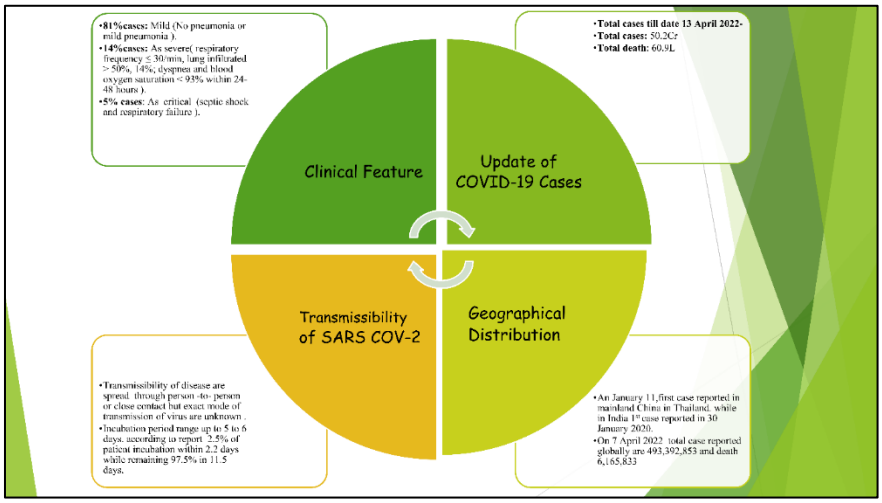


Fig. 4: Epidemiological description of covid-19 [18] (Ahmad *et al.* 2021)

Pathophysiology of covid-19 viral infection

Coronaviruses are single-stranded RNA viruses responsible for respiratory, gastrointestinal and neurological problems in human beings and many other mammals such as cats, dogs, chickens, pigs, cattle and birds. The most prevalent of them are HCoV-*229E* (Human coronavirus *229E*), OC43 (Organ Culture 43), NL63 (Netherland 63), and HKU1 (Hong Kong University 1) and all of them can cause symptoms of the common cold in immunocompetent patients. SARS-CoV-2 is the third coronavirus which has been spread worldwide over the last two decades, causing serious health issues in people [21]. SARS-Coronavirus-2 is likely to utilise receptor recognition processes similar to those used by previous virulent coronaviruses like SARS-Co-Virus, the pathogen that caused the SARS pandemic in 2003 [22]. The spike protein of the coronavirus aids virus entrance into target cells. The SARS-CoV spike component and the SARS CoV-2 spike subunit both use ACE2 (angiotensin-converting enzyme 2) as an entrance receptor (fig. 5) [23]. Additionally, cell entry needs the cellular serine protease TMPRSS2 or other proteases which activate the spike protein [24]. For this entrance procedure to be completed, ACE2 and TMPRSS2 must be co-expressed on the cell surface. Furthermore, as evidenced by investigations of SARS-CoV, the virus's ability to attach to ACE2 is a major factor in transmissibility [25]. Recent research has found that SARS-CoV-2 has a stronger affinity for ACE2 when compared to SARS-CoV, which could help to explain the increase in the transmissibility SARS-CoV-2 [26, 27].

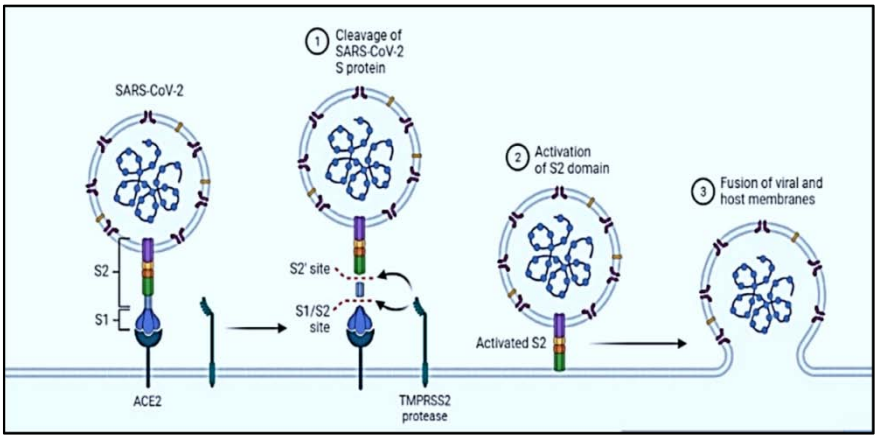


Fig. 5: Pathophysiology of COVID-19 infection [23] (Lan *et al.* 2020)

Preventive approaches

As they say, "Prevention is better than cure," so preventive measures such as breaking the chain through social distancing, making awareness and understanding in people to wear masks like N95, Double Masking (one surgical Mask and one triple-layer Cloth Mask), maintaining cleanliness, gargling with warm water, inhaling a stream, home quarantine, and movement restrictions can help to prevent spreading of COVID infection. Proper hand sanitization and cleanliness might help to prevent the infection from spreading [28].

Various treatment approaches

In the treatment of COVID-19, there was a rush to use experimental medicines and drug repurposing to combat this novel viral infection at the start of the outbreak. Since then, global clinical research studies have led to innovative medicines and vaccine candidates' development at an extraordinary pace, great progress has been accomplished in handling COVID-19. Antiviral treatments (*e. g.,* ritonavir combined with molnupiravir, nirmatrelvir and remdesivir), anti-SARS-CoV-2 monoclonal antibodies (e. g., sotrovimab), anti-inflammatory drugs (e. g., dexamethasone), and some immunomodulators agents (e. g. baricitinib, tocilizumab) are currently accessible for COVID-19 treatment [29]. However, not every COVID-19 patient is eligible for treatment with any of these drugs. Depending on the severity and existence of risk factors, the potency of these treatments varies. This sickness occurs in two phases: the early phase is responsible for the SARS-CoV-2 replication at its peak and it lasts with the beginning of symptoms, and the late phase includes replication at its lowest point. Antiviral medicines and some treatments based on the application of antibodies are expected to be more useful during this phase [30]. Various covid-19 treatments are summarised below:

Repurposing drug candidates

In cases of covid-19 treatment, various repurposed drugs are used to treat the illness; some examples of these drugs are:

Remdesivir

Gilead Sciences produced Remdesivir, a new antiviral medication that was originally developed to cure Marburg virus infections and EBOLA. Remdesivir is a prodrug containing nucleotide analogue that is converted to an adenosine triphosphate analogue inside the cell, which inhibits viral RNA polymerases. Remdesivir has a broad-spectrum activity against members of various virus families, including filoviruses (such as Ebola) and coronaviruses (such as SARS-CoV and MERS-CoV), and has also shown preventive and remedial effects in nonclinical models of these coronaviruses [31]. Remdesivir also has efficacy against SARS-CoronaVirus-2 during *in vitro* testing and their effective concentration value (EC50) is 1.76μM. Remdesivir has been expected to be active against the recent omicron variant (B.1.1.529). Several clinical trials examining the application of remdesivir to cure COVID-19 are now underway or in the works. Remdesivir's pharmacokinetics in children are now being studied in a clinical investigation (NCT04431453) [32].

Ivermectin

It is an anti-parasitic medicine authorized by the Food and Drug Administration (FDA) for curing helminthiases, onchocerciasis, and scabies. The ability of this drug to reduce the incidence of malaria infection by causing the death of mosquitos that bite people and cattle is also under trial. Ivermectin is generally well tolerated and has been widely employed for various indications. The FDA has not approved ivermectin to be employed in the treatment of any viral illness [33]. Ivermectin was reported to inhibit SARS-CoV-2 in *in vitro* research, with a single addition to Vero-hSLAM cells 2 h after infection with SARS-CoV-2, resulting in a 5000-fold reduction in viral RNA at 48 h. This is due to the virus's immune evasion mechanism being disrupted by suppressing IMP/1-mediated nuclear drift of viral proteins. To assess its involvement in the therapy of COVID-19, more *in vitro*, *in vivo*, and clinical research is needed [34].

Lopinavir/ritonavir

Lopinavir or ritonavir, was the first to come into existence for inhibiting human immunodeficiency virus (HIV) and was also used for two decades in the treatment of SARS and MERS as a repurposed drug [35, 36]. In a recent study aimed at comparing the effectiveness and safety of present-day treatments for SARS and MERS, besides COVID-19, LPV/r-based combos exhibited greater virological eradication and radiological improvement, as well as a lower rate of acute respiratory distress syndrome (ARDS). Because of the absence of any proven effective therapies, LPV/r is widely utilized to combat the COVID-19 pandemic from the start and is being studied in numerous clinical trials till today, including the World Health Organization's Solidarity trial, which began on March 20 [37].

Hydroxychloroquine and chloroquine

In 1934 the antimalarial medication chloroquine was first created. After some years, hydroxychloroquine, a chloroquine derivative was created in 1946. In addition to malaria, hydroxychloroquine is also employed to cure autoimmune illnesses such as systemic lupus erythematosus and rheumatoid arthritis. The drug has also been claimed to inhibit the replication of SARS-CoV-2 during the *in vitro* experiment. Chloroquine is commonly used to treat malaria in places where there is a pandemic. Chloroquine is not extensively used in malaria-free countries. Chloroquine and hydroxychloroquine have very similar chemical structures and mechanisms of action. According to an FDA report, the main safety concern to the use of chloroquine/hydroxychloroquine is the generation of heart rhythm problems in COVID-19 patients [38].

Molnupiravir

It is a direct-acting, broad-spectrum oral antiviral drug. Molnupiravir targets the RNA-dependent RNA polymerase (RdRp) enzyme. It was initially developed as a drug to treat viral infections such as influenza, alphaviruses, and horse encephalitic viruses, including Eastern, Western, and Venezuelan encephalitic viruses. A notable drop in hospitalization and death in mild COVID infection was seen in an analysis of available phase 1-3 studies of Molnupiravir. Early treatment with the drug also lowers the risk of hospitalization or mortality in non-vaccinated people having mild-to-moderate COVID-19 infection [39].

Convalescent plasma therapy

Antibodies from a healed patient's blood are used in convalescent plasma therapy to treat those who are severely ill [40]. The therapy can also be used to immunize those who are at high risk (health workers, patients' contacts and their families). It was used to treat SARS, the 2009 H1N1 influenza A pandemic, H5N1 avian influenza A, various hemorrhagic fevers, including Ebola, and many more viral illnesses. Convalescent plasma has emerged as the brightest ray of hope to preserve human lives against the COVID-19 in a time when all conceivable therapeutic options are being researched to save the huge loss of human lives all over the world. Convalescent plasma has previously been used in other recognized therapies, but in this case, it has been tried and shown to be effective, and the practices at other locations have demonstrated that it has the same high degree of efficacy and safety [41].

Immunomodulatory agents

Interleukin (IL)-1 antagonists

For the treatment of rheumatoid arthritis an IL-1 receptor antagonist, anakinra is sanctioned by the FDA. Anakinra was found to lower the demand for invasive mechanical ventilation and reduce the probability of death in patients who are severely infected with coronavirus in a small case-control study-based trial, which included 52 patients who got anakinra and 44 patients who act as a standard of care. For the three novel SARS-CoV-2 types, there is a lack of data on the efficacy of IL-1 receptor antagonists (B.1.1.7, P.1 and B.1.351). Due to a lack of data, this medication is not advised to treat COVID-19 infection nowadays [42].

Interferon-β-1a (IFN-β-1a)

SARS-CoV-2 inhibits the generation of interferons, which are cytokines that are necessary for preparing an immunological response against viral infection. Previous use of IFN-1a in the treatment of ARDS (acute respiratory distress syndrome) has not

been beneficial. It was seen in a small double-blind, randomised, placebo-controlled experiment, that inhaled IFN-1a have a higher chance of clinical improvement and recovery than the placebo. A small randomised clinical trial found that inhaled IFN-1a did not differ substantially from the control group in terms of clinical response. The scientists reported that when this drug was used early in the hospitalisation process, a shorter duration of hospitalization and a lower death rate was seen. However, the results were difficult to interpret as 4 patients in the treatment group died before finishing the treatment [43].

Corticosteroids

Corticosteroids have good pharmacological effects on the control of exuberant and dysfunctional systematic inflammation. Generally, in the prevention of lung injury that occurs due to severe community-acquired pneumonia corticosteroids are used. Glucocorticoids' efficacy in COVID-19 patients was not well understood during the early stages of the pandemic. Due to the absence or less availability of scientific data from large-scale randomised clinical studies, it was a source of discussion and uncertainty [44]. The recovery trial, which included hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 who were randomly assigned to receive dexamethasone or usual care, found that mortality rate reduces in patients receiving dexamethasone along with invasive mechanical ventilation and oxygen support, but not in patients who were not on any respiratory support. According to a survey, dexamethasone is now in the standard treatment procedure for hospitalised patients who require supplementary respiratory support, either alone or in combination with other drugs such as remdesivir, depending on the seriousness of the infection [45].

Monoclonal antibodies

IL-6 is a cytokine that is thought to be the main mediator of the hyperinflammatory condition caused by COVID-19. Tocilizumab, a recombinant humanised anti-IL-6 receptor monoclonal antibody, has been used in patients with COVID-19 and cytokine storm and has been proven to be effective. Some case reports show that targeting this cytokine with an IL-6 receptor inhibitor help in slowing down the inflammatory process giving positive results in individuals with severe infection. The FDA approved three different types of these inhibitors which include-Siltuximab, Tocilizumab and Sarilumab [46].

Sarilumab and siltuximab

They both are IL-6 receptor antagonists. They may have a similar effect as that of tocilizumab on the COVID-19-related hyperinflammatory state. Currently, no published study is available that supports the application of siltuximab in patients with a serious infection. On the other hand, a 60-days randomised, double-blind placebo-controlled global phase three trial evaluated the efficacy and safety of sarilumab in 431 patients, resulting in no meaningful enhancement in clinical efficacy and mortality rate. Another randomised, double-blind research for the evaluation of the clinical efficacy and safety of sarilumab in adult COVID-19 patients is now underway (NCT04315298) [47].

Tocilizumab

Tocilizumab is a monoclonal antibody that targets the interleukin-6 receptor's alpha receptor and has been used to treat a number of rheumatic illnesses. The pieces of evidence supporting the usage of this agent are inconsistent. A randomised control study involving more than 400 hospitalised patients with severe COVID-19 pneumonia, results in finding that there is no notable enhancement in clinical status or a reduction in 28-day mortality in patients treated with tocilizumab when compared to placebo [48].

Vaccination for prevention of COVID-19

To prevent a pandemic, many efforts have been made to develop COVID-19 vaccines, with the S-protein of the virus being used in the majority of developing vaccine contenders. The global SARS-CoV-2 vaccine landscape as of July 2020 consists of above 150 vaccine candidates, more than135 of which are in the preclinical stage of research. Various vaccines used for COVID-19 are summarised below (fig. 6) [49]. The vaccination activates our immune system resulting in the generation of neutralising antibodies against coronavirus. More than 2.4 billion vaccine doses have been given as of June 22, 2021, according to the WHO Coronavirus Dashboard, with more than 22% of the world's population receiving at least one shot of the vaccine [50].

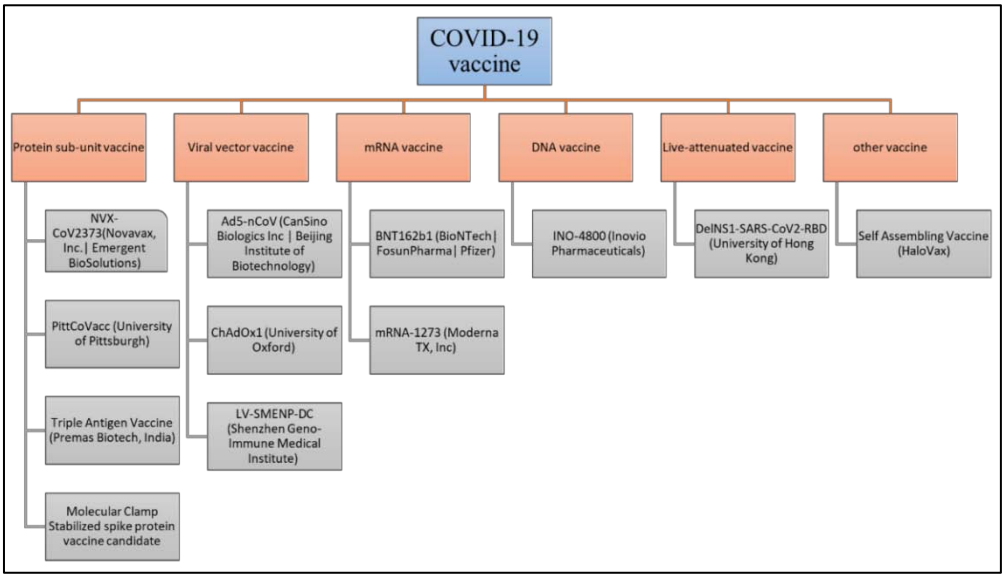


Fig. 6: Classification of vaccines used for COVID-19 [49] (Horby *et al.* 2021)

Protein subunit vaccine

A protein subunit vaccine is made up of synthetic peptides or recombinant antigenic proteins that give a preventive and curative immune response that lasts for a long time period. Protein subunit vaccines are made up of harmless and purified viral components (proteins) that have been chosen for their capacity to induce immunity [51].

Novavax

Novavax (NVX-CoV2373) is an immunogenic nanoparticle vaccine based on the recombinant expression of the S-Protein of coronavirus, a stable pre-fusion protein. The two vaccine components stimulate both B-lymphocyte and T-lymphocyte immune responses to the S protein of the virus. The full-length S protein in this vaccine comprises similar epitopes that may

safeguard us against all COVID virus strains. Furthermore, when maintained at conventional refrigerated conditions of 2-8 °C, the vaccine is found to be stable, with a 9-month shelf life [52].

PittCoVacc

It is a Micro-Needle Array (MNA) based vaccine containing recombinant immunogens, namely, rSARS-CoV-2 S1 and rSARS-CoV-2-S1fRS09 [53].

Triple antigen vaccine

Premas Biotech of India has developed the first triple antigen virus-like particle vaccine candidate. In the development of this vaccine, they clone and transform segments from the coronavirus gene into a highly characterized *S. cerevisiae*-based D-Crypt™ platform, inducing Covid-specific neutralising antibodies in BALB/mice. In this vaccine, three proteins, namely spike, membrane and envelope co-expressed and self-assembled into a virus-like particle (VLP) [54].

Molecular clamp vaccine

Molecular Clamp is a type of clamp that is used to hold molecules together. Candidate vaccine with a stabilised spike protein. The University of Queensland is working on it in partnership with GSK and Dynavax. The vaccine adjuvant platform technology (AS03 Adjuvant system) will be used by the university, which is thought to improve vaccine performance and reduce vaccine dose requirements [55].

Viral vector vaccine

The viral vector vaccine was first reported by Jackson and his colleagues in 1972 by applying recombinant DNA from the SV40 virus by genetic engineering. These viral vector-based vaccines estimate safety, efficacy, attenuation, genetic stability for pre-existing immunity, and genotoxicity [56].

Ad5-nCoV

Ad5-nCoV is an aerosolized recombinant vaccine that expresses the recombinant spike protein of the virus. The cloning technique was used to make this vaccine that optimizes the full-length S protein gene and plasminogen activator signal peptide genes (E1 and E3 genes). [57, 58]. A strong IgG and neutralizing antibody response are induced after 28 d of intramuscular injection of the Ad-5-nCoV dose of aerosolized booster vaccine [59].

ChAdOx1(AZD1222)

The Jenner Institute at the University of Oxford created ChAdOx1, an adenoviral vaccination vector. The vector is a chimpanzee adenovirus that has been engineered to prevent replication. ChAdOx1 is a potential vaccine vector that could be utilized to deliver vaccine antigens to people who need high cellular immune responses to be protected. Adenoviruses are effective vectors for eliciting and enhancing cellular immunity to recombinant antigens that have been encoded [60].

LV-SMENP-DC

Lentiviral vaccines are made via infecting dendritic cells with a lentiviral vector and employing SMENP minigenes to protect the SARS-CoV-2 protein and protease domains. APCs trigger cytotoxic T cells, resulting in an immunological response [61]. The safety of this candidate is currently being evaluated in phase 1/2 multicenter trial in healthy people and people having COVID-19-infection (>6 mo), adults, and the elderly. The project is currently recruiting participants, with results expected in 2024 [62].

mRNA vaccine

BNT162b1 (Pfizer)

The trimerized SARS-CoV-2 receptor-binding domain, a major target of the viral nAb, is encoded by the BNT162b1 codon which optimizes the mRNA vaccine [63]. It is composed of lipid nanoparticles containing nucleoside-modified mRNA (modRNA) expressing a mutant variant of SARS-full-length CoV-2's spike protein [64].

Moderna (mRNA-1273)

In February 2020, Moderna Pharmaceuticals announced the availability of their first experimental mRNA COVID-19 vaccine, which is geared up for human trials. By May 2020, the business notified that the vaccination has developed antibodies in all 45 healthy volunteers in the initial clinical phase, ranging in age from 18 to 55. The USFDA gave the business authorization to launch a phase 2 investigation of its vaccination candidate in early May, and the company commence a phase III clinical trial after July [65].

DNA vaccine

INOVIO-4800

It is a prophylactic DNA vaccine effective against SARS coronavirus. It is a nucleic-acid-based vaccine that is stable at room temperature for years. It does not require frozen transport or years of storage, which is why it is considered a vital vaccine candidate when mass vaccinations are being implemented [66, 67].

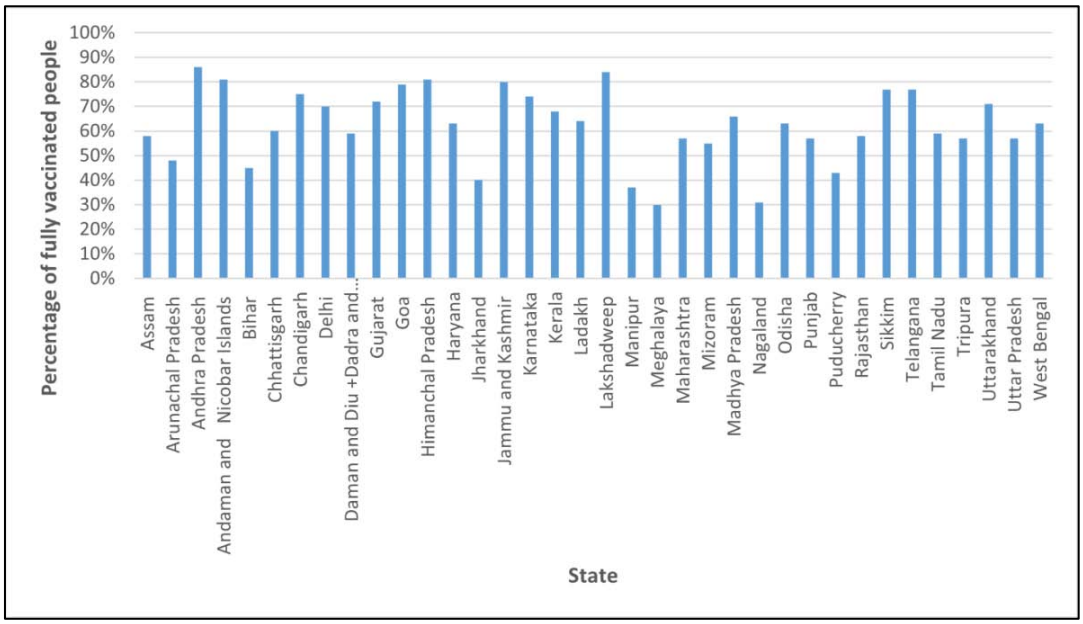


Fig. 7: State-wise trends of fully vaccinated people in India [71] (Dashboard. cowin. gov. in. 2022)

Live attenuated vaccines

DelNS1-SARS-CoV2-RBD

This LAV is an influenza vaccination strain with an NS1 gene deletion. It has been restructured to express the RBD domain of the SARS-CoV-2 spike protein on its surface and is cultured in chick embryos and/or Madin Darby Canine Kidney Cells (MDCK) cells. It may be administered as a nasal spray and may be more immunogenic than the wild-type influenza virus [68].

Others

ICMR, NIV AND Zydus Cadila (India): Bharat Biotech collaborated with two pharmaceuticals company: the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV), to manufacture the COVAXIN. ZyCoV-D vaccines were developed by Zydus Cadila [69].

Covid-19 vaccination programme of India

India started administering COVID 19 vaccine on January 16, 2021. As of March 12, 2022, India had delivered about 1.8 billion doses of the presently authorized vaccines, including first, second, and precautionary (booster) doses [70]. Table 1 includes data collected from the government database regarding the status of vaccination in different states and union territories of India. According to the official data, Andhra Pradesh has the most fully vaccinated people among all the states of India. Most of the people vaccinated come under the age group of 18-44 y (fig. 7, fig. 8) [71].

Table 1: Data of COVID-19 vaccination programme in India up to April 2022

State	Population of state (2021)	Total dose administered (1st+2nd dose)	Percentage of people administered with 1st dose	Percentage of people administered with 2nd dose	Percentage of people given a booster dose	Ref.
Assam	3,50,43,000	4,41,08,370	67%	58%	8.5%	
Arunachal Pradesh	15,33,000	16,61,893	59%	48%	1.7%	
Andhra Pradesh	5,27,87,000	9,16,01,179	84%	86%	3.3%	[72]
Andaman and Nicobar Islands	4,00,000	6,73,811	85%	81%	2.7%	
Bihar	12,30,83,000	12,53,11,385	56%	45%	0.7%	
Chhattisgarh	2,94,93,000	3,81,32,208	68%	60%	1.5%	
Chandigarh	12,08,000	20,69,213	94%	75%	2.3%	
Delhi	2,05,71,000	3,26,65,454	87%	70%	2.4%	
Daman and Diu+Dadra and Nagar Haveli	10,17,000	13,83,954	76%	59%	0.9%	
Gujarat	6,97,88,000	10,62,41,271	77%	72%	3.4%	
Goa	15,59,000	26,88,474	91%	79%	2.1%	
Himanchal Pradesh	73,94,000	1,26,57,164	88%	81%	2.8%	
Haryana	2,94,83,000	4,19,25,799	79%	63%	0.9%	
Jharkhand	3,84,71,000	3,85,45,187	59%	40%	0.7%	
Jammu and Kashmir	1,34,08,000	2,21,88,773	83%	80%	2.5%	
Karnataka	6,68,45,000	10,41,63,888	80%	74%	2.1%	
Kerala	3,54,89,000	5,34,22,020	79%	68%	3.3%	
Ladakh	2,97,000	4,58,561	79%	64%	1.1%	
Lakshadweep	68,000	1,21,352	90%	84%	3.9%	
Manipur	31,65,000	27,91,397	49%	37%	2.1%	
Meghalaya	32,88,000	24,06,938	42%	30%	0.9%	
Maharashtra	12,44,37,000	16,16,43,267	72%	57%	1.5%	
Mizoram	12,16,000	15,39,761	70%	55%	2.2%	
Madhya Pradesh	8,45,16,000	11,61,37,387	70%	66%	1.1%	
Nagaland	21,92,000	15,77,477	40%	31%	0.1%	
Odisha	4,56,96,000	6,38,59,111	74%	63%	2.0%	
Punjab	3,03,39,000	4,10,17,236	77%	57%	1.5%	
Puducherry	15,71,000	16,43,905	61%	43%	0.9%	
Rajasthan	7,92,81,000	10,29,10,219	70%	58%	1.9%	
Sikkim	6,77,000	11,27,395	85%	77%	4.7%	
Telangana	3,77,25,000	6,12,81,235	84%	77%	1.5%	
Tamil Nadu	7,64,02,000	10,32,00,246	75%	59%	0.9%	
Tripura	40,71,000	52,07,673	70%	57%	1.8%	
Uttarakhand	1,13,99,000	1,72,23,568	77%	71%	3.8%	
Uttar Pradesh	23,09,07,000	30,09,89,663	72%	57%	1.1%	
West Bengal	9,81,25,000	13,55,44,428	73%	63%	2.0%	

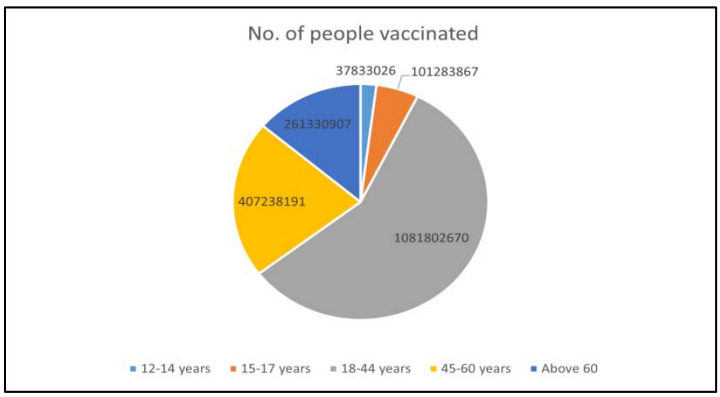


Fig. 8: Age-wise trend of vaccination in India [71] (Dashboard. cowin.gov.in. 2022)

CONCLUSION

As we all know that this COVID-19 pandemic is a health disaster and crisis of global level concern and the time requires that all the countries need to come on the same tangent and carry forward a coordinated effort to fight COVID. When there was no vaccine and antivirals against coronavirus, isolation and quarantine achieved remarkable results. But as the research on this virus proceeds with time, treatment strategies, including repurposed drugs such as antiviral and antimalarial drug, helps in mitigating the virus. Currently, many vaccines have been developed all over the world and some of them have already been given under emergency use to a large number of people. Rapid vaccination programmes have played a vital role in controlling the number of death that occurs due to this lethal infection. So, it is required to strengthen our health system to monitor the progress of COVID-19 with time. It is also necessary in today's world to find out the old approved drugs that can be repurposed for the treatment of COVID-19 and develop vaccines against this infection as soon as possible.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

There is no conflict of interest among all the authors of this article.

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