



Coronavirus Disease 2019 (COVID-19): Review on Transmission, Clinical Presentations, Treatments and Vaccines

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SAR and SS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SM managed the analyses of the study. Author AM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has become one of the most prevalent and significant global health concerns since its origin in Wuhan, China in the December 2019. As on 05th April, this disease has affected over 131 million people and has resulted in more than 2.85 million deaths worldwide till date. The disease is transmitted from the infected patients to the people in close contact through respiratory droplets. There are a number of factors which affect the transmission of this disease. The clinical presentation of COVID-19 can range from asymptomatic infections to critical disease leading to respiratory failure, septic shock and multiple organ failure. The disease

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essentially affects the respiratory system but other organ systems may also be involved. Currently, the therapeutic management of the disease is based on the severity of the infection and employs various strategies like monoclonal antibodies, corticosteroids, antivirals, stem cell therapy and immunomodulators. Scientists and researchers all around the world have raced against the time and developed a number of vaccines for COVID-19. At present, there are many COVID-19 vaccines, which have been authorized or approved for use by the regulators of the different countries. This article reviews the current published data on the COVID-19 transmission, clinical presentations, treatments and vaccines.

Keywords: COVID-19; clinical presentations; transmission; treatment; vaccines.

1. INTRODUCTION

Many respiratory disease outbreaks encountered in the past are due to coronaviruses (CoVs), making them the major disease-causing pathogens. CoVs belong to the family of single-stranded RNA viruses (+ssRNA) whose shape is found to be spherical or pleomorphic, roofed with a club shaped glycoprotein [1]. Coronavirus disease 2019 (COVID-19) caused by a highly infectious virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic and is posing a serious threat to the global public health [1,2]. SARS-CoV-2 is a betacoronavirus and is closely linked to SARS virus as depicted by genetic sequencing. The past incidences have shown that some viruses have the ability to cross species barriers and can infect human beings through animals or birds that can serve as intermediate hosts and can cause common illnesses like common cold to more severe diseases in some cases [2]. Seven CoVs of zoonotic origins have crossed the species barrier so far, to cause infections in humans, and three of them have caused deadly infections in last two decades, including the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2. SARS-CoV-2 is believed to be originated from bats and spread to other hosts such as snakes and pangolins before causing infection in humans.

Studies have shown that many factors, including environmental and patient related factors, influence the transmission and infection of SARS-CoV-2. However, till date, the exact mechanisms of transmission of SARS-CoV-2 have not been fully understood. Human-to-human transmission of SARS-CoV-2 from infected patients or asymptomatic carriers can take place through two ways [3]. The first way

can be directly through the close contact with an infected person (<2 meters) wherein the respiratory droplets can enter through mouth, eye, nose, or airways. The other can be indirect way by touching an infected object, surface, or hand of a person previously contaminated with respiratory secretions and subsequently touching own's mouth, eye, or nose [4].

Common clinical manifestations of COVID-19 are fever, dry cough, fatigue, difficulty in breathing, nasal congestion and in some cases diarrhoea and vomiting. Intensive care unit (ICU) support with mechanical ventilation may also be required in severe cases, as the virus is known to cause respiratory failure. Multiple organ dysfunction syndromes (MODS), septic shocks are also seen in critical cases [5]

At present, prevention and control of infection, supportive care with oxygenation and mechanical ventilation are the mainstay measures for the COVID-19 clinical management. A number of pharmacologic interventions including antiviral therapy, corticosteroid therapy immunosuppressive therapy, antibody therapy, stem cell based therapy and antithrombotic therapy have been used for the clinical management of COVID-19. However, currently only remdesivir, an antiviral drug, has been approved by the US Food and Drug Administration (FDA) for COVID-19 treatment [5-7]. Scientists and researchers all around the world have raced against the time and developed a number of vaccines for COVID-19. Currently, there are many COVID-19 vaccines, which have been authorized or approved for use by the regulators of the different countries. However, mere having the approved vaccines is not sufficient to control this global pandemic. In order to achieve the global control of this pandemic, the vaccines should be produced at a mass scale, reasonably priced and delivered to the local communities in a timely manner.

2. SIMILARITIES AND DIFFERENCES OF SARS-COV-2 FROM OTHER VIRUSES

The three variants of coronaviruses (SARS, MERS and SARS-CoV) that caused severe respiratory disease outbreaks displayed several unique features having similarities and differences [6]. SARS-CoV-2 is having a similar genomic sequence as SARS-CoV (approximately 90% identity). Both these diseases were originally originated from bats which serve as natural reservoir of these viruses. Host cell receptors used by SARS-CoV and SARS-CoV-2 are the same. SARS-CoV-2 shows greater affinity than SARS-CoV in binding to the receptor cells of the host [8]. This explains why SARS-CoV-2 spreads more easily than the SARS virus. However, the earlier outbreaks, SARS and MERS have shown significantly higher case fatality rates in comparison to COVID-19. But SARS-CoV-2 is more infectious in comparison to SARS and MERS which is quite evident by the number of people it has infected worldwide. COVID-19 infected individuals have high viral load in the nose and throat whereas in SARS the viral load peaks much later after contracting the sickness [9]. This shows that people with COVID-19 can transmit the virus during the course of the infection even during symptom development and before their condition worsen. As per report, COVID-19 can easily spread by people who are asymptomatic and not displaying any symptoms. SARS-CoV displayed significant person to person transmission and also very hard to control making it a pandemic [7]. But compared to SARS and MERS, COVID-19 is less pathogenic with mortality rate of 3.4% as against 9.6% with SARS. Researchers have found that COVID-19 virus mutates more than the earlier variants [8,9].

3. TRANSMISSION OF SARS-COV-2

Coronaviruses are enveloped viruses having one positive-stranded ss RNA and can mutate and recombine and are very diverse in nature. They belong to family *Coronaviridae* and classified into four genera; Alphacoronaviruses (α), Betacoronaviruses (β), Gammacoronaviruses (γ) and Deltacoronaviruses (δ). The viral genome encodes for four structural proteins: spike (S), envelope (E), membrane (M), and the nucleocapsid (N) [10].

Genus Coronavirus includes around has 40 different types of strains and mainly infect non-human mammals, birds and humans. Spiked glycoproteins, or peplomers give coronaviruses the corona-like appearances which makes it

possible for the viruses to attach firmly the host cells.

Following is the possible mechanism by which it causes infection to the host [10]:

1. The coronavirus approaches the semipermeable membrane of epithelial cells.
2. S1 subunit present at the distal region of the glycoprotein spike of the virus first binds to a membrane-bound angiotensin-converting enzyme-2 (ACE-2) receptor.
3. After binding to ACE-2 receptor, conformation change in the S protein occurs which leads to fusion of viral envelope with the cell membrane following endosomal pathway.
4. After entering in the host cell, SARS-CoV-2 releases its genetic material into the host cell.
5. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases.
6. The polymerase enzyme generates a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins.
7. Viral proteins and genome RNA are then subsequently assembled into virions in ER and Golgi and then transported out of the cell via vesicles and infect other cells.

These all steps are shown in flowchart below (Fig. 1).

4. FACTORS AFFECTING COVID-19 INFECTION

The pandemic diseases are believed to be affected by various patient and environment related factors that can directly or indirectly affects its transmission or spread (Fig. 2). A number of articles and studies have shown the effect of patient related specific characteristics that could lead to an increase or decrease in susceptibility to SARS-CoV-2. Moreover, studies have summarised the effect of various environmental conditions on the survival rate of SARS-CoV-2. All these factors are discussed in detail below.

4.1 Age

The studies have shown that two groups of people (older people over 60 years old and people with underlying health conditions) have

greater risk of infection with SARS-CoV-2. As per CDC report from China, people over the age of 60 years are at increased risk of developing severe symptoms from SARS-CoV-2. In addition, an increase in mortality rate in elderly is due to comorbid conditions like hypertension, kidney, and cardiovascular diseases [11]. Similar report from U.S. stated that about 31-59% of adults aged 60 years and above were diagnosed positive with the virus in comparison to 14-21%

of patients aged 20-44 years [11]. As per the reports, children are at lesser risk of getting infected by this deadly virus (Fig. 3) [11]. The possible reasons could be the presence of cross-protective antibodies produced as a result of multiple upper respiratory tract infections initiated by common cold-causing alpha coronaviruses. Another reason is fewer ACE-2 receptors in lower respiratory tract of children, which do not bind with S proteins of beta coronaviruses.

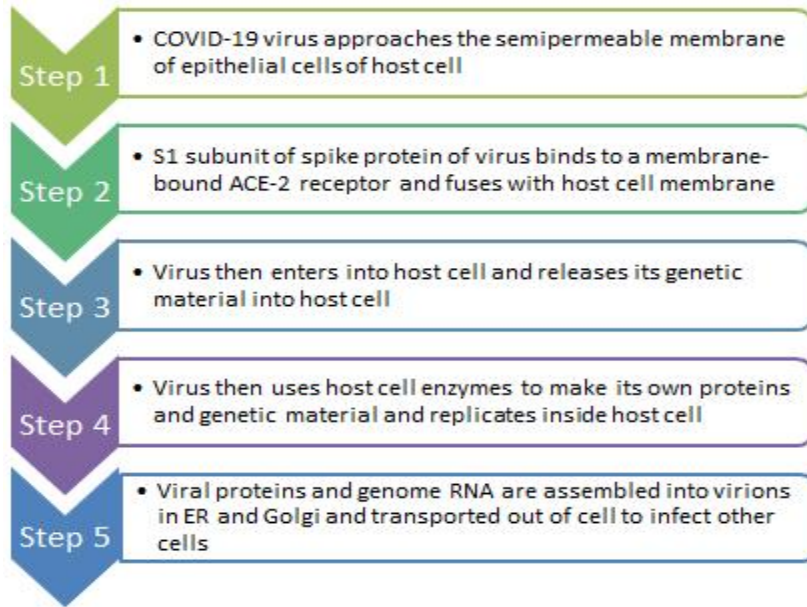


Fig. 1. Mechanism of transmission of COVID-19 in host cells

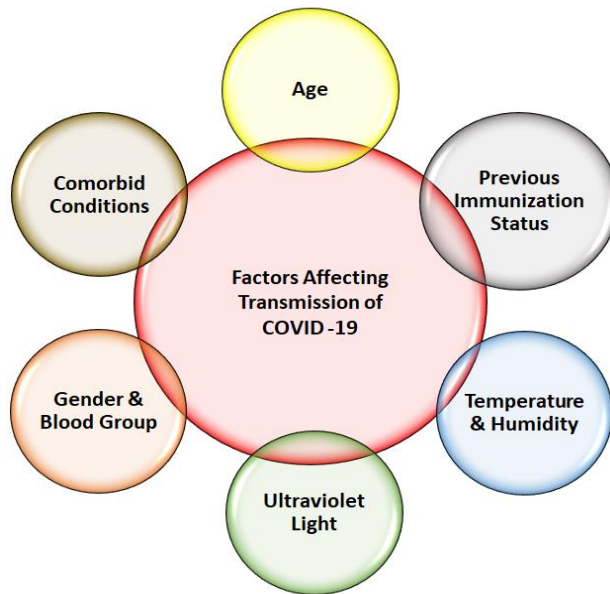


Fig. 2. Factors affecting transmission of COVID-19

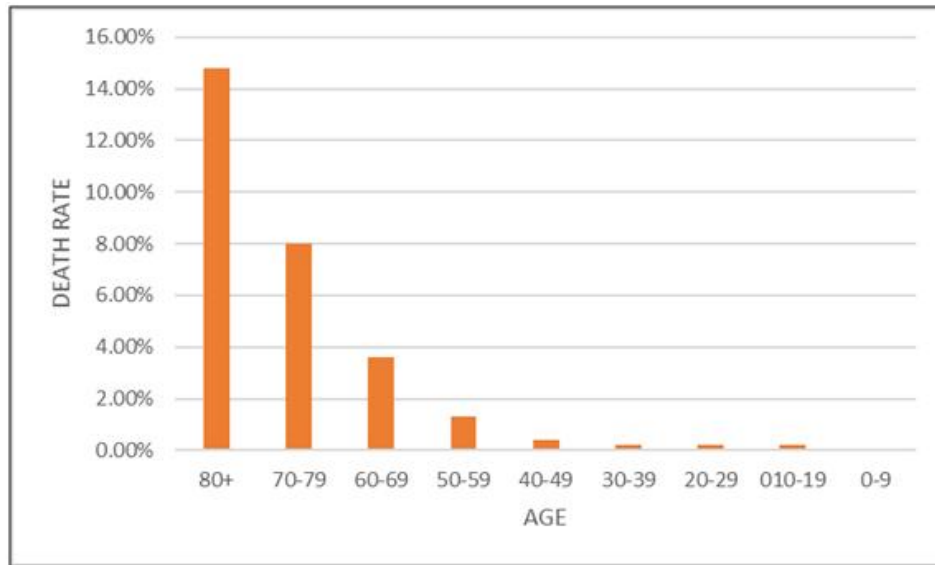


Fig. 3. Relationship between age and death rate in COVID-19

4.2 Diseases/Medical Conditions

Studies have shown that people with existing health conditions such as hypertension, diabetes or cardiovascular diseases are more prone to this infection and likely to encounter severe symptoms of COVID-19 leading to higher mortality rate than other people who have no underlying diseases (Table 1). Hospitalization is seen to be more frequent in case of people who have underlying medical conditions. Such diseases could disrupt the functioning of vital organs and body's immune system that then fail to combat the virus. Prevailing chronic lung disease and social habits such as smoking and vaping, can cause significant lung damage and result in severe COVID-19 symptoms. Patients with diabetes are at higher risk of serious COVID-19 complications and even mortality [12]. One possible reason for it is that high blood sugar could weaken the body's immune system and makes it less capable to fight off infections. Another explanation is that the people having type 1 or type 2 diabetes can develop diabetic ketoacidosis when infected with virus, a life-threatening concern causing the blood to become too acidic. Such situations could lead to sepsis and septic shock and ultimately death [13]. Also people suffering from HIV/AIDS have a weak immune system and must be more cautious towards preventing coronavirus infection. Such individuals have low CD4 count (<200 copies/cell) with high viral load or a recent opportunistic infection.

4.3 Gender

In most countries, data indicates that men have been 50-80% more likely to die following COVID-19 diagnosis than women. A study done in China depicted that 58% of patients hospitalized with COVID-19 were male [12]. Similar pattern was observed in patients in the US and Italy too. Some researchers believed that this pattern might be due to men's social habits that (many don't wash their hands as often) makes them more prone to contract the viral disease and resulted in increased number of hospitalization. Moreover, some habits such as smoking that is more common in men, can cause serious complications if get infected by COVID-19 due to underlying respiratory problems. Men are believed to have weak immune system and have more underlying health related issues than women. The reason might be that women have two X chromosomes which may have some protective role against infection [14].

4.4 Ultraviolet Light

Coronavirus is sensitive towards ultraviolet (UV) light and heat. The previous literature suggests that the ultraviolet light can effectively destroy viruses, bacteria and fungi. Therefore, UV light can be utilized for decontaminating surfaces infected by the SARS-CoV-2 virus by bringing photodimers in the genomes of microorganisms. The Purple Sun E300 Focused Multivector Ultraviolet (FMUV) system with Shadow less

Table 1. Relation between different medical conditions and COVID-19 cases

Medical conditions	Confirmed cases of COVID-19	Death rate (all cases)
Cardiovascular disease	13.2 %	10.5%
Diabetes	9.2%	7.5%
Chronic Respiratory disease	8.0%	6.3%
Hypertension	8.4%	6.0%
Cancer	7.6%	5.0%
No pre-existing conditions	-	0.9%

Delivery TM is an automated system that has proven to decontaminate the surfaces against the COVID-19 coronavirus in 90 seconds. Ultraviolet susceptibility is calculated by D90 value which tells about the required ultraviolet dose for 90% inactivation. The range of D90 values for coronaviruses is 7-241 J/m² the mean of which is 67 J/m², should adequately represent the ultraviolet susceptibility of the SARS-CoV-2 (COVID-19) virus [15].

4.5 Temperature and Humidity

It has been claimed in several studies that temperature has a direct effect on survival of coronavirus [16]. As coronaviruses have an enveloped surface with a lipid bilayer and spike proteins, this outer oily coat hardens to a rubber kind form in colder conditions. In this manner, virus could survive for a longer period in colder regions. Almost all enveloped viruses are prone to variations in outside environment. The previous studies have proved that at temperature range of 21-23°C (70-73°F) and at relative humidity of 40% and on hard surfaces like plastic and stainless steel, SARS-CoV-2 has the survival rate of up to 72 hours. Life span of virus is inversely proportional to temperature and humidity [17]. The scientists found that a one degree Celsius elevation in temperature with one percent higher relative humidity could reduce the "R" by 0.0383 and 0.0224, respectively. "R" is the effective reproductive number of the virus. If R value falls below 1.0, it indicates that the virus is dying off faster than it is reproducing [18].

4.6 Previous Immunizations

Countries in which people have received the bacillus Calmette-Guerin (BCG) as tuberculosis vaccination had fewer cases of COVID-19 and lesser mortality rate. Countries like Italy, Netherlands and US that do not have any universal vaccination programs and country like Iran where vaccination programs are too new to reach the elderly population have been hit the hardest by the disease. Researchers in several

countries like Australia and the Netherlands are doing trials to establish the relation between BCG vaccination and occurrence of COVID-19 infection.

BCG vaccine is a live attenuated strain isolated from *Mycobacterium bovis* and is used throughout the world to provide immunity against tuberculosis. A number of countries like Japan and China have adopted BCG immunization strategy for newborns. BCG inoculation fundamentally expands the emission of supportive of cytokines, specifically IL-1beta, which has been appeared to assume an essential role in antiviral immunity. Presence of BCG antibodies inside the body could be related to reduced mortality rates in COVID-19 patients. However, BCG injection is contraindicated in immunocompromised people and pregnant women [19].

4.7 Blood Type Groups

In a study conducted in China, it was concluded that people who have type A blood are at higher risk of COVID-19 than other blood groups [20]. Chinese researchers conducted a study on 2173 patients infected with COVID-19 virus in 3 hospitals of Wuhan and Shenzhen. They performed detailed analysis of their blood samples and done comparison with the two general populations based on blood groups. Analysis of the data found that the people with blood group A are at increased risk for COVID-19 than non-A blood groups. The blood type distribution of normal population in Wuhan was type A - 31%, type B - 24%, type AB - 9%, type O - 34%, and the blood type distribution of COVID-19 patients from Wuhan was type A - 38%, type B - 26%, type AB - 10%, type O - 25%. This study suggested that people with the blood group A were at higher risk of COVID-19 infection than people with blood group O [21].

The linkage of blood groups with many diseases like heart attacks, stroke have been established by many researchers. The studies have shown

that AB type of people are at higher risk of stroke and cognitive impairment than other blood groups. In another case, it was seen that type O group provide protection against heart attacks and blood clots in the veins [22].

5. STAGES OF TRANSMISSION OF COVID-19

A global health crisis has been created due to the COVID-19 pandemic. It has affected almost every country and territory in the world. Countries have been divided into different stages according to the level of spread of the COVID-19 infection.

5.1 Stage 1 (Imported and Sporadic Cases)

As described by WHO, the disease is introduced to the population in this stage from the people who are travelling from the infected countries and are carriers for the disease. This is confirmed by testing them. The disease is not spread locally in this stage.

5.2 Stage 2 (Local Transmission)

In second stage there is local transmission from infected people. SARS-CoV infected people who travelled abroad infects those people come into contact with them. Few people are affected in this stage and the source of the virus is known. Therefore, it is easy to perform contact tracing and the virus can be contained via self-quarantining.

5.3 Stage 3 (Community Transmission)

In this stage community transmission happens. The people who are not exposed to any infected person or in contact with any person with international travel history starts testing positive. It is not possible to identify from where people might have got infected.

5.4 Stage 4 (Epidemic)

This is the worst stage. In this stage a lot of people get infected and it is very difficult to regulate and contain the spread. The virus takes the form of an epidemic. This is what China dealt with.

6. CLINICAL MANIFESTATIONS OF COVID-19

Patients with COVID-19 have a wide range of clinical manifestations and their spectrum range

from asymptomatic infections to severe disease leading to mortality [23,24]. The respiratory system is the most commonly affected but other systems can also be affected by the virus [23]. The common clinical features of COVID-19 include fever, dry cough, dyspnea, sore throat, myalgia, loss of smell (anosmia) or taste (dysgeusia), headache, chills, nasal congestion, nausea, vomiting and diarrhoea (Fig. 4) [25].

6.1 Asymptomatic Manifestations

Patients with asymptomatic COVID-19 have no clinical signs and symptoms of the disease. Their radiological examinations, like x-ray and CT chest, show no apparent abnormalities. However, their reverse transcriptase-polymerase chain reaction (RT-PCR) show positive detection of SARS-CoV-2. Early detection of asymptomatic patients and contact tracing are critical in controlling the spread of COVID-19. Nevertheless, most asymptomatic patients do not seek appropriate medical care and contribute to rapid spread of COVID-19. The asymptomatic COVID-19 patients pose a significant challenge to infection control.

6.2 Respiratory Manifestations

The common respiratory symptoms associated with COVID-19 are dry cough and difficulty breathing.²³ Patients with severe disease may progress to acute lung injury and acute respiratory distress syndrome. The patients may also present with reduced blood oxygen saturation.²¹ Bilateral ground glass opacity has been reported as the most common radiological abnormality in the computed tomography (CT) scans of the COVID-19 patients [26].

6.3 Ear, Nose and Throat Manifestations

The common ENT manifestations of COVID-19 include sore throat, loss of smell (anosmia) or taste (dysgeusia), rhinorrhea, nasal congestion, tonsillitis and dizziness [23,27].

6.4 Cardiac Manifestations

Studies suggest that cardiac manifestations are common in COVID-19 patients, particularly hospitalized patients, and are associated with poor prognosis and increased mortality [28-30]. Hospitalized COVID-19 patients can have myocardial injury particularly in the right ventricle. Impairment in left ventricular diastolic function and right ventricular function have also been reported in COVID-19 infected patients [29].

6.5 Gastrointestinal Manifestations

It has been reported that the prevalence of gastrointestinal symptoms in COVID-19 patients can range between 16 to 33% [31] however; it can go up to 50% also [32]. Among the gastrointestinal symptoms associated with COVID-19, loss of appetite (anorexia) is the most common followed by diarrhoea, nausea or vomiting and abdominal pain. Studies have reported that COVID-19 patients with gastrointestinal manifestations have shown higher rates of severe disease [33].

6.6 Renal Manifestations

COVID-19 patients may have varied degree of renal manifestations. COVID-19 associated renal manifestations reported in different studies include hyperkalemia, increased serum creatinine, increased blood urea nitrogen, proteinuria, hematuria, low glomerular filtration rate and acute kidney injury [34,35].

6.7 Neurological Manifestations

During the course of COVID-19 infection, most of the patients develop neurological manifestations in addition to respiratory manifestations. Current published data show that headache, dizziness and anosmia are the common neurological symptoms associated with COVID-19. Other reported symptoms are confusion, altered consciousness, seizure, stroke, encephalopathy and Guillain-Barre syndrome [36,37].

6.8 Musculoskeletal Manifestations

Musculoskeletal symptoms have been seen in 15 to 36% of the COVID-19 patients. The common reported musculoskeletal manifestations are generalized weakness, myalgia, fatigue, and arthralgia [38,39]. Myositis and rhabdomyolysis have also been reported [40].

6.9 Hematological Manifestations

A number of hematological manifestations associated with COVID-19 have been identified. These manifestations include blood count anomalies and COVID-19 associated coagulopathy. Common blood count anomalies reported are lymphopenia (35% - 83%), neutrophilia, thrombocytopenia, elevated lactate dehydrogenase and hyperferritinemia. Coagulation abnormalities in COVID-19 patients can manifest in the form elevated D-dimers,

prolonged PT, prolonged APTT and elevated fibrinogen [41,42].

6.10 Ophthalmic Manifestations

Ophthalmic manifestations are not very common among the COVID-19 patients but studies have reported many ophthalmologic findings including conjunctivitis with conjunctival hyperemia, irritation of the eyes, increased ocular secretions, foreign body sensation, epiphora and blurred vision [43,44].

6.11 Dermatological Manifestations

A range of dermatologic manifestations associated with COVID-19 have been identified with different case reports from all over the world, among the ones identified, include erythematous/morbilliform rash, pernio (chilblain)-like acral lesions, urticaria, vesicular eruptions and livedo reticularis lesions [45,46].

7. CLINICAL SPECTRUM OF COVID-19

COVID-19 has a wide clinical spectrum ranging from asymptomatic disease with no symptoms at all to critical disease that could lead to respiratory failure, septic shock, and multiple organ failure requiring mechanical ventilation and support in an intensive care unit [5]. Based on severity and occurrence of symptoms the disease can be as classified as [6].

7.1 Asymptomatic Disease

Patients who do not present with any symptoms of COVID-19 but test positive for SARS-CoV-2. These patients should be monitored for the signs and symptoms for a period of 14 days after the exposure.

7.2 Mild Disease

Patients who present with different clinical manifestations of COVID-19 like fever, cough, sore throat, loss of taste and smell, tiredness, headache, muscle pain, nausea, vomiting, diarrhoea but not having shortness of breath, difficulty in breathing, or abnormal chest radiological findings. These patients can be managed at home with the help of remote medicine or telephonic consultations. Patients with comorbidities are at higher risk of progression of the disease and should be monitored closely for the entire duration of the illness.

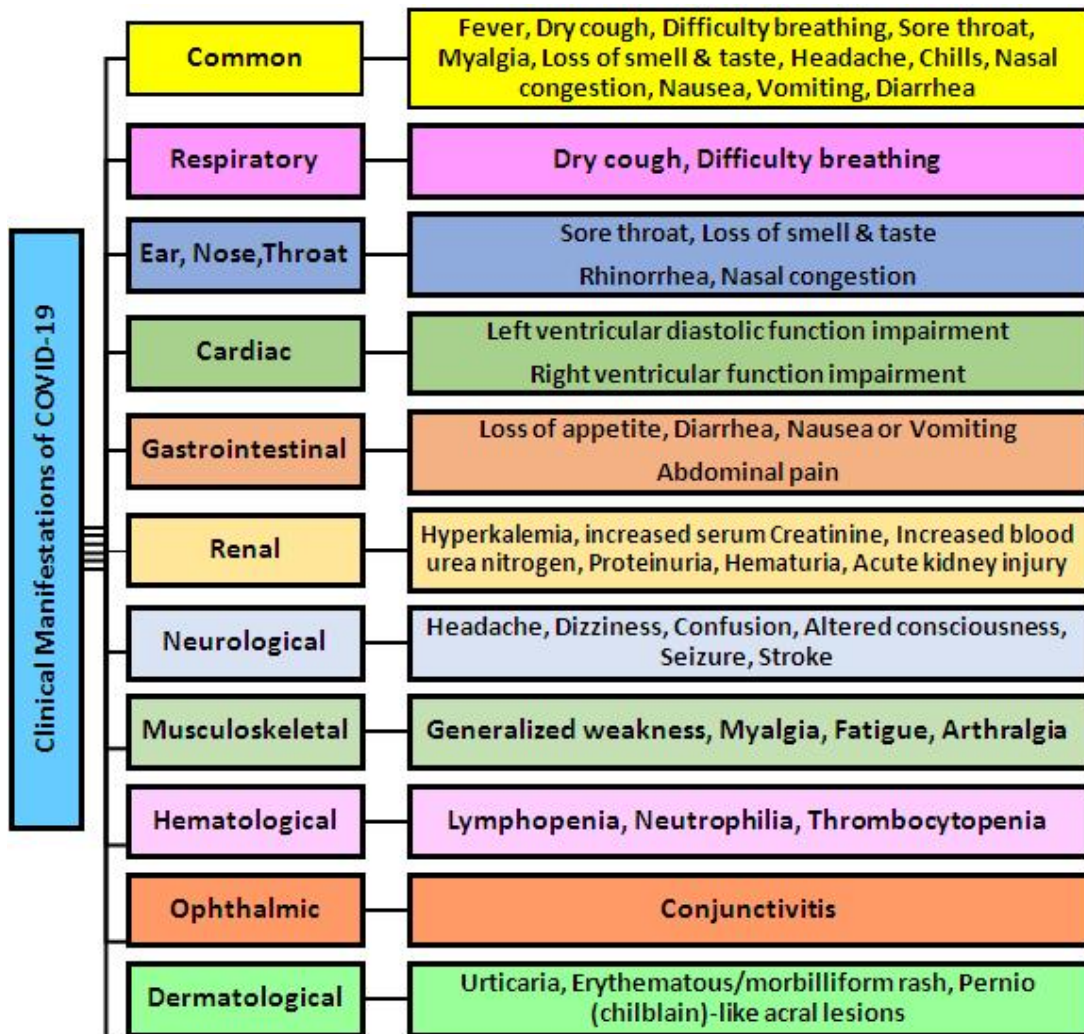


Fig. 4. Clinical manifestations of COVID-19

7.3 Moderate Disease

Patients with lower respiratory disease confirmed on clinical assessment or radiological findings with oxygen saturation (SpO₂) ≥ 94%. These patients should be monitored for progression closely on a daily basis and should be managed with appropriate pharmacologic interventions.

7.4 Severe Disease

Patients with respiratory rate >30 breaths/min, oxygen saturation (SpO₂) <94%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, or lung infiltrates >50%. Rapid clinical deterioration can be seen in patients with severe disease.

These patients should be managed with appropriate oxygenation, ventilation and pharmacologic interventions.

7.5 Critical Disease

Patients with respiratory failure, septic shock, and/or multiple organ failure. Critically ill COVID-19 patients should be managed under intensive care in line with the international recommendations with appropriate hemodynamic and ventilatory support.

8. TREATMENT STRATEGIES

Currently, prevention and control of infection, supportive care with oxygenation and mechanical ventilation are the mainstay measures for the

COVID-19 clinical management. A number of pharmacologic interventions including antiviral therapy, corticosteroid therapy immunosuppressive therapy, antibody therapy, cell based therapy and antithrombotic therapy have been used for the clinical management of COVID-19.

Based on specific pathways, the therapies to treat the corona virus can be divided into several categories [47,48]:

- a) Therapies which can prevent the viral RNA synthesis. Replication therapy is given to act on enzymes or functional proteins, which are significant to virus.
- b) Drugs that act upon structural proteins of virus and prevents the virus from binding to human cell receptors or they can inhibit the virus's self-assembly process.
- c) Drugs that helps to restore host's innate immunity.
- d) Drugs that bind to host's specific receptors or enzymes, thereby prohibiting the viral entry into host's cells.

Some of the drugs used for the clinical management of COVID-19 are listed below and are summarised in Table 2.

8.1 Chloroquine and Hydroxychloroquine

Studies on use of chloroquine and hydroxychloroquine for the management of COVID-19 have reported conflicting results. Currently, the National Institutes of Health (NIH), US recommends against using chloroquine or hydroxychloroquine with or without azithromycin for the management of COVID-19 [45]. These drugs are basically used for the treatment of malaria and arthritis. They have been used for the treatment of SARS or MERS but there is a lack of clear or high quality evidence to show their efficacy. The required dosing of chloroquine used for the management of COVID-19 is 500 mg orally once or twice a daily [49]. A study based on pharmacokinetic modelling recommended that the optimal dosing regimen for the hydroxychloroquine in COVID-19 treatment is a dose of 400 mg twice daily for 1 day followed by the 200 mg twice daily [50]. The mechanism of action (MOA) of these drugs is that they seems to block viral entry into cells by causing inhibition of glycosylation process of host cells, proteolytic processing and endosomal acidification. Also, these drugs depict immunomodulatory function by causing cytokine

generation and inhibition of autophagy and lysosomal activity in the host cells [51]. They also prevent viruses from binding to the human cells and entering inside them. They can be combined with azithromycin for positive patient outcomes. Their administration needs close medical supervision for observing side effects such as QTc interval prolongation. These drugs are not recommended for the children less than 12 years, pregnant and lactating women.

8.2 Antiviral Drugs

8.2.1 Lopinavir/Ritonavir

Currently, the NIH, US recommends the usage of lopinavir/ritonavir and other HIV protease inhibitors for the management of COVID-19 [6]. However, these drugs are still clinically used in different countries for the management of COVID-19. These agents act by causing inhibition of enzyme 3-chymotrypsin-like protease during *in-vitro* studies [7]. The commonly used dosage for COVID-19 treatment is 400 mg/100 mg two times a day for 14 days [52]. Their usage could cause side effects such as nausea and diarrhoea (up to 28%) and hepatotoxicity (2%-10%). These adverse effects could occur in 20-30% patients which might be due to elevated transaminase levels that result in transaminitis leading to liver injury in COVID-19 patients.

8.2.2 Favipiravir

The drug was first used against COVID-19 in Wuhan, China. It has received emergency use in a number of countries like Italy, Japan, Saudi Arabia, United Arab Emirates, Russia, Ukraine, and others. It has been found to be effective against coronaviruses and influenza viruses. This drug is being widely used in China and Japan for the management of COVID-19 patients. More than 300 patients were tested for the efficacy of favipiravir in COVID-19 and clinical trials were carried out in Wuhan and Shenzhen. This drug shorten the course of treatment from 10 days to a period of 4 days. This drug mainly inhibits the viral replication. It is first transformed into an active phosphoribosyl form inside the cells and inhibits RNA polymerase activity [53]. The recommended loading dose is 2400 mg to 3000 mg every 12 hours (two times a day) continued by a maintenance dose of 1200 mg to 1800 mg every 12 hours. This drug has a minor adverse effects that is well-tolerated even at higher doses.

Table 2. Summary of drugs used in COVID-19

S.No.	Drug	Category	Dose	Mechanisms of action	Side effects
1	Chloroquine (4-aminoquinoline)	Anti-malarial	500 mg orally once or twice	Endosomal acidification; glycosylation of host receptors; immunomodulatory effects by attenuating of cytokine production and inhibition of autophagy	Increases QTc interval. Toxicity Not suitable for pregnant and children under 12 years
2	Hydroxychloroquine	Anti-malarial	200 mg twice daily.	Same as that of chloroquine	Less side effects than chloroquine.
3	Remdesivir (monophosphate prodrug)	Anti-viral	200-mg loading dose, followed by 100-mg daily infusion.	Inhibits viral replication by inhibiting the RNA-dependent RNA polymerase.	Increased liver enzyme level causing liver damage, not suited for pregnant and lactating women.
4	Lopinavir/Ritonavir	Antiviral	400 mg/100 mg twice daily for up to 14 days	Protease inhibitors, Blocks viral cellular entry	Gastrointestinal distress such as nausea and diarrhea.
5	Favipiravir	Antiviral ; anti-influenza	Loading dose: 2400 -3000 mg every 12 hours × 2 doses), maintenance dose: 1200 mg to 1800 mg every 12 hours	Inhibits viral replication by inhibiting RNA polymerase inhibitors; Inhibits viral RNA-dependent polymerase	Mild side effects,
6	Ribavirin	Guanine analogues	500 mg orally every 12 hr	inhibits viral RNA-dependent RNA polymerase, Inhibits viral RNA synthesis and mRNA capping	Anaemia, hematologic and liver toxicity.
7	Umifenovir (Arbidol)	Antiviral	200 mg orally every 8 hours	Target S protein/ACE2 interaction, Fusion inhibitor ;Inhibits fusion between viral and cellular membrane	Very less side effects even at high doses. Some drug interactions are observed.
8	Tocilizumab, Sarilumab Eculizumab	Monoclonal antibody	324 mg subcutaneously of Tocilizumab,	IL-6 inhibitor, blocks cytokine storm.	Mild side effects such as allergic reactions, weakness, muscle ache, nausea and vomiting
9	Interferon-β1	Cytokines	5 million by vapor inhalation twice a day along with ribavirin	Stimulate innate antiviral immunity.	Mild side effects such as flu like symptoms, chills, fever, nausea, vomiting

8.2.3 Umifenovir

It is also known as Arbidol and is mainly used to treat influenza. This antiviral agent has a unique mechanism of action as it targets the S protein or viral interaction with ACE-2 receptor interaction and inhibiting the membrane fusion of an envelope of virus. It is considered both a direct-acting antiviral (DAA) and host-targeting agent

(HTA) due to direct virucidal effects on one or multiple stages of viral life cycle for e.g. attachment, internalization [54]. It is a broad-spectrum antiviral drug because of its dual activity. Antiviral activity is due to its interactions with aromatic residues within the viral glycoproteins which is involved in fusion and cellular recognition which could interfere with intracellular trafficking and lead to clathrin-

mediated exocytosis. Russia and China has approved this drug for the treatment of influenza and there is an increasing interest for treating COVID-19 because of its *in-vitro* activity against SARS [55]. The current oral dose is 200 mg every 8 hours for influenza or studied for COVID-19 treatment. A non-randomized study in 67 patients with COVID-19 found that the treatment for a median duration of 9 days was associated with lower mortality rates and higher discharge rates compared with patients who did not receive the agent. Even at high doses the drug is safe and no pathological changes were observed in animal models on chronic administration of doses, 10-50 times the therapeutic human dose [55].

8.2.4 Antiviral EIDD-2801

MK-4482/EIDD-2801 has been repurposed for use in COVID-19. It is an orally active antiviral drug and has shown promising results during laboratory scale experiments with human lung and airway cells and found to be effective against various RNA viruses. This drug molecule is found to be more effective against SARS-CoV-2, than the popular drug remdesivir. Its mechanism of action is quite different from remdesivir that prohibits the replication of the novel coronavirus completely. The new compound EIDD-2801 acts differently by causing genetic mutations in the viral RNA. When this faulty RNA replicates, lots of damaging mutations occur this could prevent the virus from causing further infection in healthy cells [56].

8.2.5 Ribavirin

It is an analogue of guanine which inhibits the viral RNA-dependent or RNA polymerase. It has been found to be effective against coronavirus but its use is limited due to very high dose i.e. 1.2 g to 2.4 g orally every 8 hours which can cause serious side effects [57]. Ribavirin can cause severe dose-dependent hematologic toxicity in patients when used for longer period. The haemolytic anaemia was seen in more than 60% of patients when very high doses of ribavirin was used during clinical trials. This drug is also contraindicated in pregnancy due to its teratogenic effects.

8.2.6 Remdesivir

Remdesivir has been approved by US FDA for the management of COVID-19 in hospitalized adult and pediatric patients more than 12 years

of age [6]. The drug is widely being used in the US, China, India and Italy and has been a promising potential therapy for critically ill patients. Chemically, it is a monophosphate prodrug which is an analogue of an active C-adenosine nucleoside triphosphate that undergoes metabolism. Based on the data collected from *in-vitro* cell line and mouse model, remdesivir could interfere with the NSP12 polymerase even in the setting of intact ExoN proofreading activity. The RNA-dependent RNA polymerase which is a key viral enzyme is chiefly inhibited by this antiviral drug. This drug has been broadly used against SARS-CoV-2 with EC50 and EC90 values of 0.77 μ M and 1.76 μ M [58]. This drug blocks SARS-CoV-2 infection at micromolar concentrations and has a high selectivity index which is half-maximal effective concentration and the half-cytotoxic concentration. The single 200 mg loading dose is a current dose under investigation which is followed by the daily infusion is 100 mg. There are increased liver enzyme level causing liver damage which is not suited for the pregnant and lactating women which is a side effect of the drug [58].

8.3 Interferon- α

Interferons (IFN-I) belong to the class of cytokines which are classified into α , β subtypes, ϵ , ω and κ subtypes [59]. Interferons are secreted by special cell types chiefly plasmacytoid nerve fibre cells after recognition by receptors present on semi permeable membrane when they are exposed to viruses [60]. The interferon fixation on IFNAR receptors causes relocalization to the cell nucleus, where they can cause activation of interferon-stimulated genes (ISG). Such genes are involved in causing inflammation, signaling and immunomodulation and activate the adaptive immunity [61]. IFN-I plays a significant role in antiviral immunity. For the treatment of COVID-19, the recommended dose of IFN α is 5 million by vapor inhalation twice a day to the patients, in combination with ribavirin. Moreover, Interferons were tested in various clinical trials along with antiviral drugs for treating COVID-19 patients and shown positive results with better efficacy [62].

8.4 Monoclonal Antibodies

Another adjuvant therapy used for treating COVID patients includes the use of monoclonal antibodies which works against inflammatory cytokines produced as a result of the immune

response. The rationale behind their usage lies in the underlying pathophysiology in which significant damage occurs in the lungs and other organs due to the amplified immune response and cytokine release, or so called “cytokine storm.” As seen in early cases of COVID-19, IL-6 appeared as a key component of this dysregulated inflammation reactions. Thus, monoclonal antibodies could prove to be effective against these cytokines and can slow down the whole process to improvise clinical outcomes. Most people recovering from SARS-CoV-2 infection will generate a cellular and humoral immune response against SARS-CoV-2. One FDA approved monoclonal antibody, Tocilizumab, IL-6 receptor antagonist, has been used for treating RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. With the previous experiences, tocilizumab was tested in small number of critically ill COVID-19 patients and promising results were observed. Other monoclonal antibodies tested in clinical trials include bevacizumab (anti-vascular endothelial growth factor medication), fingolimod (immunomodulator approved for multiple sclerosis), and eculizumab (antibody inhibiting terminal complement) [63]. Mild side effects were observed with the use of monoclonal antibodies that include allergic reactions, weakness, muscle ache, nausea and vomiting. Monoclonal antibody-based therapy using a combination of casirivimab and imdevimab has received Emergency Use Authorisation by the FDA in November 2020.

8.5 Ivermectin

Ivermectin is an anti-parasitic drug and has shown antiviral activity against various viruses such as human immunodeficiency virus (HIV), Dengue fever, influenza and Zika virus. Due to its promising results against various viruses, this drug could also be beneficial against SARS-CoV-2. The antiviral activity is purportedly due to the inhibition of importin (IMP) α/β Integrase which helps in the nuclear import and propagation of infection of RNA viruses [16,17]. Based on this, researchers have proposed the use of ivermectin as an add on therapy for COVID-19 treatment [64].

8.6 Corticosteroids

Corticosteroids such as hydrocortisone and dexamethasone, are used as an adjuvant therapy in some cases in treating COVID-19

patients. They act by decreasing the host inflammatory responses in the lungs, which causes acute lung injury and acute respiratory distress syndrome (ARDS). This is due to their anti-inflammatory, antifibrotic, and vasoconstrictive effects. In a recent clinical trial, the effect of dexamethasone was evaluated and the treatment was found significant reduction in 28-day mortality in patients requiring oxygen therapy or mechanical ventilation [65].

But these drugs have several adverse effects that include delayed viral clearance and increased risk of secondary infection. In short, the potential risks and lack of proven use of corticosteroids restrains their routine use in patients with COVID-19 unless a concomitant compelling indication, such as chronic obstructive pulmonary disease exacerbation or refractory shock exists [66].

8.7 Convalescent Plasma Therapy

Convalescent plasma therapy is found to be efficacious during the outbreak of SARS, MERS and also H1N1 influenza viruses. Evidence suggests that convalescent plasma collected from patients who have recovered from COVID-19 contains receptor binding domain specific antibodies with potent antiviral activity [67]. Plasma therapy has been employed in treating COVID-19 patients with serious or life-threatening infection. In this therapy, plasma of the recently recovered COVID-19 patients that contains huge stock of antibodies is infused into severely sick patients. Such plasma is termed as convalescent plasma and the recovered from the patient after 2-3 weeks. The antibodies present in convalescent plasma stimulate the patient's own immune system begin destroying the virus and helps in the speedy recovery and saving the life of a critically ill patients. This treatment has been adopted by many countries like China, South Korea, USA, UK and India. The clinical studies have depicted that convalescent plasma therapy has an adequate safety profile in patients with COVID-19. However, effective titres of antiviral neutralising antibodies, optimal timing for convalescent plasma treatment, optimal timing for plasma donation, and the severity class of patients who are likely to benefit from convalescent plasma remains unclear. Multiple observational studies have been published, some on preprint servers, reporting the association between convalescent plasma and reduced mortality, hospital stay, and viral load in patients with covid-19 [67].

A randomised controlled trial of 103 patients with severe and life threatening covid-19 in China reported no effect of convalescent plasma treatment on time to clinical improvement. In that trial, a subgroup of 45 patients with severe disease, similar to patients with moderate disease in our study, showed increased clinical improvement in the convalescent plasma group [68]. The ConCOVID trial from the Netherlands, prematurely terminated after 86 patients had been enrolled, could not find any effect on mortality at 60 days, hospital stay, or disease severity at 15 days [69]. Similar kind of results was seen in clinical trial done in India on 464 adults in a multicentric randomised controlled trial [70]. Although the use of convalescent plasma seemed to improve shortness of breath and fatigue in patients with moderate COVID-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment, this did not translate into a reduction in 28 day mortality or progression to severe disease [70].

8.8 Stem Cell Therapy

For more effective management of COVID-19, new therapeutic strategies are needed to reduce the mortality rate and to make the recovery faster. Stem cell based regenerative medicine therapy could be a useful alternative for treating COVID-19 patients [71,72]. Such kind of stem cell-based regenerative therapies were initiated in China and FDA has approved the Emergency Use Authorization (EUA) of stem cell use for COVID-19 patients that has created an excitement among the medical community. Stem cells are unspecialized cells present in the human body that have the capability to produce more stem cells as well as differentiate into specialized cells of the body if appropriate signals are provided *in-vitro* or *in-vivo*. Mesenchymal stem cells (MSCs), a special type of adult stem cells have gained special attention in stem cell related therapies currently because of their immunomodulatory and regenerative potential [71,73]. MSCs can be attained in large numbers from autologous sources such as adipose tissue, bone marrow, and from allogenic sources such as cord blood and cord tissues. Moreover, MSCs are multipotent and can be cryopreserved for various purposes to be used in future. MSCs have been used earlier for some virus related diseases such as immunologic abnormality in human immunodeficiency virus, chronic hepatitis in hepatitis B virus, and acute lung injury in influenza virus [74]. Due to

immunomodulatory potential of MSCs, they can be utilized as a supportive treatment option for faster recovery of critically ill COVID-19 patients [71,72]. MSCs can balance the immune system and stop its overactivation by their powerful anti-inflammatory and immunomodulatory properties and therefore can regulate the cytokine storms.

9. COVID-19 VACCINES

COVID-19 pandemic has spread in an exponential manner throughout the world infecting millions of people across the globe. Since its outbreak, researchers all over the world are trying their level best to understand the mechanism of its pathophysiology and to find out therapeutic agents and vaccines that could cure this deadly virus [75]. Typically, it requires years of preclinical and clinical research to develop a vaccine. However, COVID-19 has forced the scientists and researchers to run against the time, to which they have also responded promptly. Currently more than 60 COVID-19 vaccine candidates are in clinical development out of which about 20 have reached the final stages of testing. Over 170 vaccines candidates are in the pre-clinical development and are being actively investigated in the animals [76].

For vaccine development, number of strategies have been used which aims at surface-exposed spike (S) glycoprotein or S protein which is responsible for neutralizing antibodies. These complex techniques make use of either full-length S protein or S1-receptor-binding domain (RBD) and expression in virus-like particles (VLP), DNA, or viral vectors [77]. SARS-CoV-2's spike (S) protein is 1273 amino acids long and is the main target of current COVID-19 vaccines. Over the time SARS-CoV-2 virus underwent various mutations in its genomes. Some variants are B.1.1.7, commonly dubbed as the U.K. variant; B.1.351, also known as 501Y.V2 or the South African variant, P.1., also known as 501Y.V3 or the Brazilian variant; B.1.427 and B.1.429, also recognized as CAL.20C or the California variant; B.1.526, or the New York variant.

At present, there are many vaccines, which have been approved and authorized for use in different settings in different countries. Some are given early use and limited use authorization; others are approved or authorized for emergency use (Table 3). Some vaccines are described below.

Table 3. Overview of the different COVID-19 vaccines

S.No.	Vaccine Name	Developer/Company	Type of Vaccine	Phase	Status of the Vaccine [78]	Efficacy	Dose
1.	Comirnaty (BNT162b2) [79]	Pfizer-BioNTech	mRNA	Phase 3	Approved for use in: Bahrain, Saudi Arabia, Switzerland Emergency use in: Argentina, Australia, Canada, Chile, Colombia, Costa Rica, Ecuador, European Union, Iceland, Iraq, Israel, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Mongolia, New Zealand, Norway, Oman, Panama, Peru, Philippines, Qatar, Serbia, Singapore, Tunisia, United Arab Emirates, United Kingdom, United States. Limited use in: South Korea	95%	2 doses, 3 weeks apart
2.	mRNA-1273 [80]	Moderna	mRNA	Phase 3	Approved for use in: Switzerland. Emergency use in: Canada, European Union, Iceland, Israel, Mongolia, Norway, Singapore, United Kingdom, United States.	94.5%	2 doses, 4 weeks apart
3.	Sputnik V (Gam-Covid-Vac) [81]	Gamaleya Research Institute	Vector	Phase 3	Early use in: Russia. Emergency use in: Algeria, Argentina, Armenia, Belarus, Bolivia, Bosnian Serb Republic, Guinea, Hungary, Iran, Kazakhstan, Lebanon, Mexico, Myanmar, Nicaragua, Pakistan, Palestinian Authority, Paraguay, Serbia, Tunisia, Turkmenistan, United Arab Emirates, Venezuela.	91.6%	2 doses, 3 weeks apart
4.	AZD1222 [82]	Oxford-AstraZeneca	Vector	Phase 3	Emergency use in: Algeria, Argentina, Bangladesh, Bhutan, Brazil, Chile, Dominican Republic, Egypt, El Salvador, European Union, Iceland, India, Iraq, Maldives, Mexico, Mongolia, Morocco, Nepal, Norway, Pakistan, Philippines, South Africa, Thailand, United Kingdom.	82.4%	2 doses, 12 weeks apart
5.	Convidecia [83] (Ad5-nCoV)	CanSino Biologics	Vector	Phase 3	Emergency use in: Mexico Limited use in: China	65.7%	Single dose
6.	EpiVacCorona [84]	Vector Institute	Peptide antigens-based	Phase 3	Early use in: Russia	NA	2 doses, 3 weeks apart
7.	BBIBP-CorV [85]	Beijing Institute of Biological Products - Sinopharm	Inactivated	Phase 3	Approved for use in: Bahrain, China, United Arab Emirates.	79.34%	2 doses, 3 weeks apart

S.No.	Vaccine Name	Developer/Company	Type of Vaccine	Phase	Status of the Vaccine [78]	Efficacy	Dose
8.	CoronaVac [86]	Sinovac Biotech	Inactivated	Phase 3	Emergency use in: Cambodia, Egypt, Hungary, Iraq, Jordan, Pakistan, Peru. Limited use in: Serbia, Seychelles. Approved for use in: China. Emergency use in: Azerbaijan, Brazil, Chile, Colombia, Indonesia, Laos, Turkey, Uruguay.	50.38%	2 doses, 2 weeks apart
9.	Covaxin [87]	Indian Council of Medical Research - National Institute of Virology - Bharat Biotech	Inactivated	Phase 3	Emergency use in: India	NA	2 doses, 4 weeks apart

9.1 Comirnaty (Pfizer-BioNtech Vaccine)

Comirnaty is a lipid nanoparticle based mRNA vaccine developed by Pfizer in collaboration with German based biotechnology company BioNtech. It is administered as an intramuscular injection and is required to be given in two doses three weeks apart. It has been approved for use in countries like Saudi Arabia, Bahrain, New Zealand and Switzerland, and has been given emergency use authorization in many countries like United States, United Kingdom, United Arab Emirates, Mexico, Malaysia and others [78]. The phase 3 randomized placebo-controlled trial of this vaccine conducted 43,448 participants showed that a two-dose regimen (doses given 21 days apart) conferred 95% protection against COVID-19 with no safety concerns [79].

9.2 mRNA-1273 (Moderna Vaccine)

mRNA-1273 is a lipid-nanoparticle-encapsulated mRNA vaccine developed by Moderna and the National Institutes of Health (NIH), United States. It is administered as an intramuscular injection and is required to be given in two doses four weeks apart. It has been approved for use in Switzerland and has been given emergency use authorization in many countries like United States, United Kingdom, Canada, Israel, Norway, Singapore and others [78]. The phase 3 randomized placebo-controlled trials of this vaccine conducted 30,420 volunteers reported that a two-dose regimen (doses given 28 days apart) showed an efficacy of 94.1% against COVID-19 with no safety concerns [80].

9.3 AZD1222 (Oxford-AstraZeneca Vaccine)

AZD1222 is an adenoviral vector (ChAdOx1) based vaccine developed at Oxford University in collaboration with AstraZeneca. It is administered as an intramuscular injection and is required to be given in two doses 12 weeks apart. It has been given emergency use authorization in many countries like United Kingdom, European Union, India, Egypt, Iraq, Kuwait, Maldives and others [78]. Initially it was reported that the two-dose regimen has 62% efficacy against the COVID-19 [82]. But the recent data from the phase 3 efficacy trials revealed that the two doses of the vaccine 12 weeks apart conferred 82.4% protection against the COVID-19 [88].

9.4 Sputnik V (Gamaleya National Research Institute Vaccine)

Sputnik is an adenoviral vector vaccine developed by the Gamaleya National Research Centre for Epidemiology and Microbiology. It is administered intramuscularly in two doses separated by 21-day interval. The vaccine has been given early use authorization in Russia and emergency use authorization in countries like United Arab Emirates, Pakistan, Bahrain, Argentina, Algeria, Kazakhstan, Mexico, Hungary, Iran and others. A randomized, placebo-controlled, multicenter, phase 3 trial of this vaccine conducted in 21, 977 adults revealed 91.6% efficacy against COVID-19 with good tolerability [81].

10. CONCLUSION

Viral diseases are the major cause of high rates of morbidity and mortality in humans. Emerging new age diseases like Ebola, AIDS, MERS, SARS and COVID-19 have created the urgency to understand various factors influencing the emergence and spread of viral diseases worldwide. COVID-19 pandemic has widely spread throughout the world affecting more than 200 countries and has become one of the most prevalent and significant global health concerns since its origin in Wuhan, China in the December of last year. The disease has proven to be fatal for the aged and comorbid population. The disease has proven to be fatal for the aged and comorbid population. The most effective approach to mitigate the spread of the virus remains the basic precautionary measures like physical distancing, wearing masks, cleaning hands regularly and avoiding crowds. To date, there is no effective therapeutic agent to treat COVID-19. Clinical management of COVID-19 still largely remains symptomatic. Many pharmacological therapies have been tried and tested including the use of antivirals, corticosteroids, immunomodulators, antibodies, and among others. This pandemic can come to end only with the mass rollout of vaccines, which will give herd immunity and offer protection against the severe disease. Currently, there are many COVID-19 vaccines, which have been authorized or approved for use all over the world. However, mere having the approved vaccines is not sufficient to control this global pandemic. In order to achieve the global control of this pandemic, the vaccines should be produced at a mass scale, reasonably priced and delivered to the local communities in a timely manner.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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