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REVIEW

Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence

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ABSTRACT

Introduction: The COVID-19 pandemic has created a public health crisis, infected millions of people, and caused a significant number of deaths. SARS-CoV-2 transmits from person to person through several routes, mainly via respiratory droplets, which makes it difficult to contain its spread into the community. Here, we provide an overview of the epidemiology, pathogenesis, clinical presentation, diagnosis, and treatment of COVID-19.

Areas covered: Direct person-to-person respiratory transmission has rapidly amplified the spread of coronavirus. In the absence of any clinically proven treatment options, the current clinical management of COVID-19 includes symptom management, infection prevention and control measures, optimized supportive care, and intensive care support in severe or critical illness. Developing an effective vaccine is now a leading research priority. Some vaccines have already been approved by the regulatory authorities for the prevention of COVID-19.

Expert opinion: General prevention and protection measures regarding the containment and management of the second or third waves are necessary to minimize the risk of infection. Until now, four vaccines reported variable efficacies of between 62–95%, and two of them (Pfizer/BioNTech and Moderna) received FDA emergency use authorization. Equitable access and effective distribution of these vaccines in all countries will save millions of lives.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious and infectious disease caused by the novel coronavirus, severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) [1,2]. It is well documented that the initial cases of COVID-19 related infection were first reported in Wuhan, Hubei Province of China in December 2019, and were linked to the Huanan Seafood Market [3]. Since then, the infection has spread to over 216 countries and territories. The World Health Organization (WHO) announced that COVID-19 reached pandemic status on 30 January 2020 [4,5] and subsequently, declared a global pandemic in March 2020 [6]. It has since been referred to be 'the most crucial global health calamity of the century and the greatest challenge that humankind faced since the 2nd World War' [7]. As of 26 December 2020, there were approximately 80,500,000 confirmed COVID-19 cases worldwide, including 1,700,000 related deaths [8], with a case fatality rate of 2.2%. The case fatality rate varies among countries, estimated from 0 to more than 20% [9]. A second wave of COVID-19 infection has already been recorded in many countries, which may be due to premature relaxation of government-enforced lockdown rules in many parts of the world [10,11]. Several countries have reported a new rise in daily cases higher than the first wave in March 2020 [12,13]. Although there is no shortage of information on this pandemic virus presented in everyday practice, this paper presents a comprehensive review of the latest information on SARS-CoV-2 highlighting the epidemiology, pathogenesis, and clinical aspects of SARS-CoV-2 infection.

2. Methods

We searched and reviewed literature published since November 2019, which focused on the epidemiology, pathogenesis, diagnosis, treatment, and prevention of COVID-19. Original studies, reviews, editorials, commentaries, perspectives, short or special communications, and position/policy papers on the COVID-19 pandemic were also searched. Information from websites of different professional associations and national or international organizations was extracted. Reference lists from the retrieved articles were also manually examined for relevant information. PubMed, Scopus, and Google Scholar were also searched using specific keywords, including 'SARS-CoV-2', 'COVID-19 infection', 'epidemiology', 'pathogenesis', 'diagnosis', 'treatment', and 'prevention'.

3. Origin, history, and epidemiology of COVID-19

Coronaviruses are a large family of viruses that are common in humans and many different species of animals (e.g. cats, bats). Most people are infected with these viruses at some point in

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Article highlights

- The COVID-19 pandemic has created a public health crisis, infected millions of people, and caused a large number of morbidities and mortalities.
- COVID-19 transmits from person to person through several routes, mainly via respiratory droplets, which makes it difficult to contain its spread into the community.
- Currently, there is no effective antibody test available, and an effective, rapid, and sensitive serological test for COVID-19 is urgently needed for rapid diagnosis.
- In the absence of any clinically proven treatment options, the current clinical management of COVID-19 includes symptom management, infection prevention and control measures, optimized supportive care, and intensive care support for severe or critical illness, and general prevention and protection measures regarding the containment and management of the second or third waves are necessary to minimize the risk of infection.
- There is some promising news regarding COVID-19 vaccines as large-scale (Phase 3) clinical trials are in progress. As of 24 November 2020, four vaccines were reported to be 62–95% effective. Equitable access and effective distribution of these vaccines in all countries will save millions of lives.

their lives. Common human coronaviruses typically cause upper respiratory tract infections (URTIs) such as the common cold. However, some variants can cause mild influenza-like symptoms. Initially, cases related to SARS-CoV-2 were associated with high mortality rates, especially in people with chronic diseases, such as diabetes and cardiovascular diseases [14,15].

There are four main genres of coronaviruses: alpha (α), beta (β), gamma (γ), and delta (δ). The first human coronaviruses were identified in the mid-1960s. Common variants that affect people around the world include 229E, NL63, OC43, and HKU1. Among them, 229E and NL63 are α-coronaviruses, and OC43 and HKU1 are β-coronaviruses [16]. The usual signs and symptoms generated by these coronaviruses are similar to those of the common cold, accompanied by mild to moderate URTI. It is also of note that some coronaviruses that infect animals can undergo mutation and adaptation, thereby driving the co-evolution of coronaviruses that can become a new human coronavirus (HCoV) [17]. Therefore, these HCoV infections are zoonotic, and their symptoms are accompanied by more severe respiratory tract syndromes than those of the aforementioned ones. Three recent examples of these are: (i) SARS-CoV-2 (the novel coronavirus, causing coronavirus disease in 2019 or COVID-19), (ii) SARS-CoV (the β-coronavirus, causing severe acute respiratory syndrome, or SARS), and (iii) MERS-CoV (the β-coronavirus, causing Middle East respiratory syndrome, or MERS) [17,18].

COVID-19 was initially thought to be a zoonotic disease originating in bats, which may have undergone several cross-species events, first crossing the species barrier to pangolins and subsequently to humans. The outbreak appeared to have started from single or multiple zoonotic transmission events in the wet market in Wuhan [19]. As such, it was initially suspected that direct contact with intermediate host animals or the consumption of wild animals was the main route of SARS-CoV-2 transmission [5]. Its epidemiological link was first demonstrated by the appearance of several reported cases of severe respiratory distress, which had a typical characteristic radiological pattern (e.g. initial chest images demonstrated multifocal airspace opacities and consolidation in 70–80% of coronavirus-infected patients [20]). SARS-CoV-2 is highly transmissible and preliminary reports have suggested that the reproductive number (R_0) of people that an infected person could potentially infect is approximately 2.2 [21]. The R_0 is used to reflect contagious disease, and the higher the number, the more infectious the disease. If SARS-CoV-2 is compared to influenza and other diseases, the high R_0, which varies from to 3–5, is representative of a more contagious infection [22,23] (Table 1). The number of COVID-19 cases increased at a rapid rate, partly due to the highly infectious nature of the virus as well as the lack of awareness and availability of diagnostic kits in the initial stages of the pandemic [24].

Table 1. Reproduction number (R_0) of some selected viruses [22,23].

Viruses	R_0
Measles	12–18
Pertussis (Whooping cough)	12–17
Chickenpox	8–9
Rhinovirus (cold)	5–7
COVID-19	3–5
Smallpox	5–7
HIV/AIDS	2–5
SARS	2–5
1918 influenza	2–3
Seasonal influenza	1–2

Mortality for COVID-19 appears to be higher than that for influenza, especially seasonal influenza. Early estimates relied heavily on genetic tests, which are the gold standard for diagnosing COVID-19, from either sputum or nose swabs from the back of the nose [25]. However, these tests only provide a clear picture of active infection; they are not an accurate reflection of possible past infective events. In addition to the genetic tests, serological studies are now also used, and can indicate whether the individual has been infected in the past, based on antibody response [26].

4. Structural and molecular features of SARS-CoV-2

SARS-CoV-2 belongs to the genus *Betacoronavirus* of the subfamily *Orthocoronavirinae* in the family Coronaviridae, and the order Nidovirales [27–30]. The viral particle is pleomorphic, as confirmed by cryo-electron tomography, and possesses non-segmented, single-stranded, positive-sense ribonucleic acid (ssRNA+) as its genome [31,32]. A coronavirus contains four structural base proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) [32,33]. Among them, the S protein plays the most important role in viral attachment, fusion, and entry [34]. Its 30 kb genome RNA is large enough to produce a positive sense to be read directly by ribosomes in the cell [33]. The genome is coated with an N protein, which forms a helical nucleocapsid [35]. The N protein-coated genome is enclosed in a lipid envelope, and the viral lipid envelope is speckled by viral proteins [35,36]. As viruses cannot make their own lipids, they use the host's lipids for replication and

morphogenesis [37]. The N protein plays a crucial role in the morphogenesis phase of the viral life cycle during virion formation [35]. In addition to the lipid envelope, coronaviruses have a membrane glycoprotein called the matrix protein on its outer layer [38]. This transmembrane protein has a significant C-terminal domain that makes contact with the N protein [39]. Another minor envelope protein, E, is also an important component at the end of the viral life cycle [38].

Coronaviruses get their name from the characteristic feature of their S protein, which resembles a halo effect seen in solar eclipse or a crown-like appearance under an electron microscope [34]. The S protein has a roughly cylindrical shape and is heavily glycosylated [40], and encodes and possesses both receptor-binding and-fusion functions. Coronavirus uses its S protein, a main target for neutralizing antibodies, to bind with specific receptors and mediate membrane fusion and virus entry. It is a trimeric protein [34], composed of three intertwined chains that have identical amino acid sequences, each of which is called a protomer. However, the protomers do not have identical three-dimensional conformations. The monomer of the trimeric S protein is approximately 180 kDa and contains two distinct functional subunits, S1 and S2, both necessary for mediating attachment and membrane fusion, respectively. In its structure, N- and C-terminal portions of the S1 fold are two independent domains, the N-terminal domain (NTD) and C-terminal domain (CTD). Depending on the virus, either NTD or CTD can serve as the receptor-binding domain (RBD). The S protein induces successful infusion into the cell by first binding to the host receptor through the RBD of the S1 subunit, resulting in viral genomic fusion; the second stage by S2 facilitates the fusion of the cell and host membranes, which contains amino acid sequences necessary for continuing infiltration [41–43]. The RBD in the S protein is the most mutable part of the coronavirus genome and tends to be common for general viruses [44].

During viral replication, SARS-CoV-2 uses host protease enzymes to covalently attach sugars to asparagine side chains near the protein surface [45]. To achieve fusion, the S protein needs to be cleaved by proteases present in the host cell. The hosts own peptide bond breaking proteases cut the S protein at specific sites, and conformational changes enable fusion to occur [46]. Moreover, the availability of proteases on target cells largely determines whether coronaviruses enter cells through the plasma membrane or by endocytosis [47]. Proteolytic cleavage of the S glycoprotein also determines whether the virus can cross species, for example, from bats to humans [48]. The process is critical because it allows the fusion sequences to be exposed. The nature of the cell protease that cleaves the S glycoprotein varies according to the coronavirus [31]. Coronavirus proteins may be cleaved by one or several host proteases based on virus strains and cell types, including trypsin, cathepsins, transmembrane protease serine protease-2 (TMPRSS-2), TMPRSS-4, or human airway trypsin-like protease (HAT) [43,49]. However, the specific proteases that promote virus entry into SARS-CoV-2 remain elusive [43,49,50]. This cleavage is generally mediated by furin [50], an enzyme belonging to the subtilisin-like proprotein convertase family. It cleaves precursor proteins and facilitates their conversion to a biologically active state; thus, it plays a vital role in viral protein processing [51]. The S1/S2 cleavage site is the target site of furin during infection. The RBD of the S1 subunit contacts angiotensin-converting enzyme 2 (ACE2), which is facilitated by furin cleavage [52,53]. Furin proteases are found in significant amounts in the lungs. Therefore, viruses that attack the respiratory tract make use of this enzyme to convert and activate their own surface glycoproteins. Basically, it is like a lock-and-key mechanism, where viral glycoprotein and cellular receptor represent key and lock, respectively. Other influenza pathogens that have similar cleavage sites can also be acted upon by furin and other cellular proteases. The prevalent expression of cellular proteases across cell types increases the potential for the virus to successfully infiltrate the host [53]. It should be mentioned here that all other β-coronaviruses, including SARS-CoV, which is the closest to the SARS-CoV-2 strain, do not contain this cleavage site [54]. A study showed that the S protein of SARS-CoV-2 is 10 to 20 times more likely to bind to human ACE2 than the S protein of the early 2000s SARS-CoV strain [55]. The heightened affinity for a prevalent cellular receptor may be a factor that increases transmission [56].

5. Mechanism of SARS-Cov-2 transmission

5.1. Mechanisms of transmission

The transmissibility of an infection is determined by the basic R_0, with a value above the threshold of 1 implies continuous and sustained human-to-human transmission [23,57]. The rapid spread of SARS-CoV-2 is due, in part, to the transmission mechanisms of the viral agent. An understanding of the transmission dynamics of infectious spread is critical, providing insights into the epidemiologic spread, implementation of outbreak control measures, and determination of the efficacy of such control measures [23].

The transmission characteristics of SARS-CoV-2 are very similar to those of SARS-CoV and pandemic influenza. Riou *et al*. [57] stated that this was an indicator of the potential for sustained human-to-human transmission and the risk of global spread. More recently, a mean R_0 range of 2.24 to 3.58 [58,59] was determined. With transmissibility on par with that of SARS-CoV, pandemic influenza, and HIV, but much lower than measles and chickenpox (Table 1), SARS-CoV-2 presented a moderate to severe infectious threat [57].

The first evidence of potential person-to-person transmission was reported by Chan *et al*. [60]. They investigated the transmission of the virus in a group of family members who had recently visited Wuhan. They had no history of contact with animals, visits to markets, or eating game meat, but stayed in the same hotel throughout their travel. With no direct zoonotic involvement, this was the first indication that the virus could be spread by human contact. These initial findings were subsequently confirmed with increasing evidence demonstrating sustained human-to-human transmission [57,61].

SARS-CoV-2 uses the same receptor, ACE2, as SARS-CoV, and mainly spreads through the respiratory tract [62]. As a respiratory infectious disease, the virus is transmitted primarily by droplets, respiratory secretions, and direct contact [63]. However, viral particles have been isolated from fecal swabs and blood, implying several alternative routes for transmission [64–66]. It is worth noting that the ACE2 protein is also expressed by enterocytes in the small intestine [67]. Previous Chinese reports have shown no evidence of vertical transmission of the virus by blood products or the fecal-oral route [64,68–70]. However, some recent studies from the United Kingdom (UK) and other countries have confirmed a low rate of vertical transmission due to COVID-19 [71–75].

5.2. Incubation period

The incubation period on average is 1–14 days, however, generally is 3–7 days. SARS-CoV-2 may be present in the throat or the nose a few days before symptom onset. Interestingly, completely asymptomatic subjects may have viral loads similar to those of symptomatic patients [76]. This implies that asymptomatic individuals may be possible sources of infection. After the incubation period, patients present with similar symptoms, including fever, cough, and malaise. A small percentage of patients also manifest gastrointestinal symptoms, such as diarrhea and vomiting. The elderly and those with underlying disorders rapidly develop acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation dysfunction, which may ultimately lead to multiple organ failure and even death [5,77,78].

6. Clinical and pathological characteristics of COVID-19

SARS-CoV-2 targets the respiratory system, and transmission occurs via contact droplets and fomites from an infected person who may be symptomatic or asymptomatic [79]. During the incubation period, the virus triggers a slow response in the lungs. SARS-CoV-2 mainly invades alveolar epithelial cells, resulting in respiratory symptoms [80].

The S-glycoprotein on the surface of SARS-CoV-2 binds to ACE2 [80]. The receptor and the enzyme on the surface of type 2 alveolar cells induce a conformational change in S-glycoprotein initiating proteolytic digestion by host cell proteases (TMPRSS2 and furin), ultimately leading to internalization of the virion [81]. This implies that SARS-CoV-2 has a pathogenesis similar to that of SARS-CoV [82]. Coronaviruses generally enter via endocytosis or direct fusion of the viral envelope with the host membrane. Once internalized by the host cell, the viral particle is uncoated, and its genome enters the cell cytoplasm. Coronaviruses have an RNA genome from which they can directly produce their proteins and new genomes in the cytoplasm by attaching to the host ribosomes [83]. The host ribosomes translate viral RNA into RNA polymerase proteins. This RNA polymerase then reads the positive strand again to generate single-stranded, negative-sense RNA (ssRNA-) strands.

The ssRNA- strands are then used as a template by RNA polymerase to make additional ssRNA+ strands. The small RNA strands are read by host ribosomes in the endoplasmic reticulum to make the structural components of the virus. These structural components are then transferred from the endoplasmic reticulum to the Golgi apparatus. Within the Golgi apparatus, ssRNA+ genomes are packaged in the nucleocapsids to create new virion particles. These progeny viruses are then released from the host cell via exocytosis through secretory vesicles. The replication of the virus in alveolar cells mediates damage and induces an inflammatory response in the tissues. Cellular entry of the virus triggers an inflammatory response by recruiting T-helper cells that produce interferon (IFN)-gamma (IFN-γ), interleukin (IL)-2, and IL-12 [84]. The injured alveolar cells also release interferons, cytokines, and other intracellular components. The subsequent recruitment of other inflammatory cells leads to the development of a '*cytokine storm*' which can precipitate the organ damage and multi-organ failure seen in severe disease [84]. COVID-19 infected patients have shown higher concentrations of peripheral blood immune mediators [85]. IL-6, interferon gamma-induced protein (IP)-10, and IFN-γ were markedly elevated in all three highly pathogenic HCoV infections [3,85]. Interferons act in a paracrine manner and can have numerous effects on the surrounding cells, preparing them against viral infection [86]. The alveolar macrophages detect cell injury and respond to cytokines released by injured alveolar cells. The alveolar macrophages respond by secreting cytokines and chemokines [87]. The inflammatory process occurring within the lung parenchyma stimulates nerve endings responsible for initiating the cough reflex, thus, people often present with an early dry cough [87]. Tumor necrosis factor (TNF)-α and IL-1β are proinflammatory cytokines that cause an increase in vascular permeability, increase in adhesion molecule expression, and induce recruitment of more immune cells, including neutrophils and monocytes. They bind to adhesion proteins on the surface of tissues and enter the site of injury [88]. IL-8 recruits neutrophils, and other chemokines attract monocytes [89]. The increase in vascular permeability causes leakage of fluid into the interstitial space and alveoli, resulting in interstitial and pulmonary edema. This can lead to dyspnea, impaired oxygenation, or hypoxemia. The clinicopathological characteristics of coronaviruses are shown in Figure 1.

Neutrophils engulf viruses and other debris around the area, which can be detrimental because this activity also results in the release of chemical by-products that damage the surrounding tissue [90]. Consequently, when there are damaged alveolar cells all over, less surfactant is produced. The alveoli can easily collapse, resulting in impaired oxygenation or hypoxemia [91] (Figure 1). White blood cells (WBCs) and damaged endothelial cells release other inflammatory mediators, including arachidonic acid metabolites, including leukotrienes and prostaglandins. Leukotrienes cause bronchoconstriction, leading to impaired ventilation, and subsequent hypoxemia [92]. Prostaglandins, IL-1, IL-6 and TNF-α are responsible for causing fever, a primary feature of COVID-19 [93,94]. Decreased oxygen levels in the blood stimulate chemoreceptors in the cardiopulmonary center in the brain, which causes an increased inspiratory rate to increase oxygen levels in the blood and also initiate the heart to pump faster to

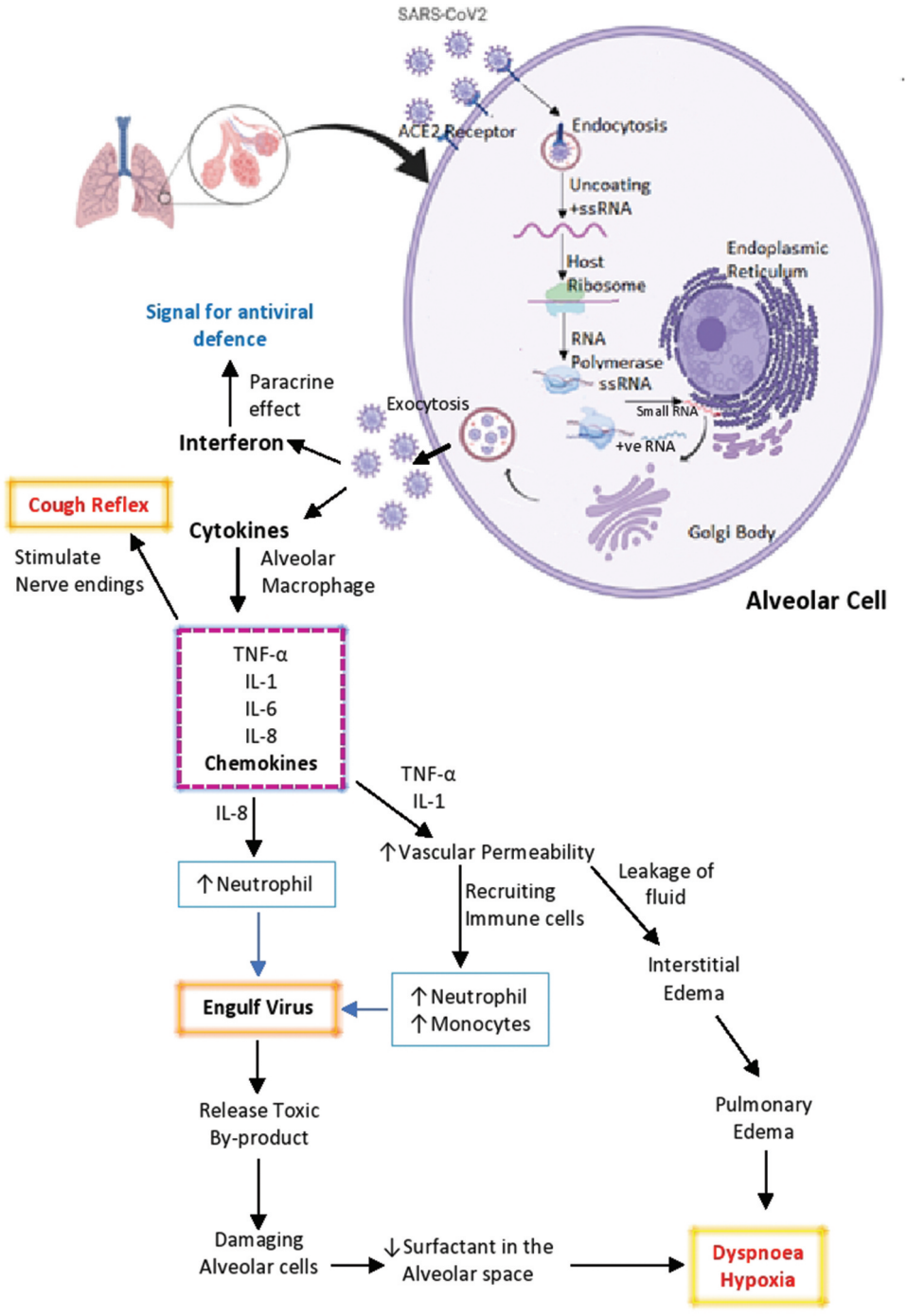

Figure 1. Viral replication of SARS-coV-2 in alveolar cells.

deliver oxygen to the body [95]. For this, patients with hypoxemia usually develop tachypnea and tachycardia [96]. However, some patients may be asymptomatic because their immune system keeps it in check or only minor symptoms, such as cough accompanied by shortness of breath and some fever. The alveolar macrophages can also detect the virus using its special toll like receptor-4 (TLR-4) receptors, which engulf viral particles through phagocytosis [97].

A common finding in COVID-19 is lymphopenia, which is assumed to be due to the release of interferons [98]. IL-6 stimulates hepatocytes to produce acute phase reactants such as C-reactive protein (CRP), fibrinogen, and hepcidin [99]. CRP is a good inflammatory marker, and a high level in the blood is a marker of inflammation [100]. Therefore, the damaged alveolar tissue, accumulation of the fluid, ventilation/perfusion mismatch, and hypoxemia, which are not related to heart function, leads to the presentation of ARDS, which is considered to be the leading cause of mortality in COVID-19 [101].

6.1. Clinical manifestations

Patients with COVID-19 experience varying degrees of severity, and 80% of them have mild infection [102]. Approximately 15% of cases develop severe disease characterized by

dyspnea, hypoxia, and lung changes on imaging; 5% are critically ill, with respiratory failure from ARDS, shock, and/or multi-organ dysfunction [3,103,104]. As ACE2 is expressed not only in the lungs but also in the heart, endothelium, renal tubular epithelium, intestinal epithelium, and the pancreas, SARS-CoV-2 may possess the potential to invade these tissues, to proliferate and destroy these organs, causing multiple organ dysfunction syndrome (MODS) [105,106]. Excessive activation of lymphocytes and increased pro-inflammatory mediators in patients with COVID-19 promotes immune-mediated damage. The process causes a mild disease to increase in severity and single organ involvement to progress to MODS. In severe cases, the disease can lead to ARDS, septic shock, metabolic acidosis, coagulation dysfunction, and MODS. Elderly individuals with reduced immunity and comorbidities are more susceptible to severe infections [107].

The median age of individuals affected by severe complications related to COVID-19 ranges from 49 to 56 years of age [108]. As symptoms progress, patients may develop pneumonia with ARDS, which requires intensive care. Children are typically asymptomatic or present with mild symptoms. Men and women have the same susceptibility to infection; however, male patients are more at risk for worse outcomes and death [109]. The symptoms include fever, fatigue, dry cough, anorexia, myalgia, dyspnea, and sputum production [110]. Mortality rate increases with age, with a significant increase above 80 years of age. The mortality rate also increased with comorbidities, including diabetes, heart disease, chronic kidney disease, chronic lung disease, and other socio-demographic factors (Table 2). An increased risk of infection due to SARS-CoV-2 is also found to be associated with other comorbidities such as hypertension (27–30%), diabetes (19%), and coronary heart disease (6–8%) [104,111]. Studies have also demonstrated that patients with severe COVID-19 develop ARDS (67.3%), acute kidney injury (28.9%), abnormal hepatic function (28.9%), and cardiac injury (23.1%) [112]. An overview of the effect of COVID-19 on different pathophysiological conditions is presented in Table 2 [109,113–124].

7. COVID-19 diagnostic techniques

The rapid and accurate detection of COVID-19 has become vital for effective response and prevention of further spread in large populations. Contact tracing has also been shown to be of extreme importance. It has allowed the systematic encapsulation of specific points of caseload increase, giving governments the opportunity to protect the health of the population without completely shutting down their economies. The American Center for Disease Control and Prevention (CDC) has been utilized since the initial identification of SARS-CoV -2 molecular assays for its detection, mostly using real-time polymerase chain reaction (PCR) methods [125]. The PCR for COVID-19 can only diagnose whether a person is currently infected with this particular coronavirus. It cannot provide information on other diseases or symptoms [126] and could miss patients who have cleared the virus and recovered from the disease [126,127]. Serology tests are also important as they can help assess the immune response [128], follow up on the progression of the disease, and the length of immune protection present after patients have recuperated from COVID-19 [129]. The serologic test is an enzyme-linked immunosorbent assay (ELISA)-based test that detects SARS-CoV-2 antibodies (IgG and IgM) in serum or plasma. The ELISA used by the CDC utilizes purified SARS-CoV-2 S protein (no live virus) as an antigen [130]. The problem with serologic tests is that the cross-reactivity to antibodies generated by other coronaviruses cannot be completely ruled out [130]. Comparative information on the use of different diagnostic techniques for COVID-19 is presented in Table 3 [131–134].

8. Treatment and preventive measures

In the absence of any clinically proven treatment options, the treatment is symptomatic, and current clinical management includes infection prevention and control measures as well as supportive care [135]. Available therapeutic drugs include antiviral agents (e.g. remdesivir, hydroxychloroquine, chloroquine) and supporting agents (vitamin C, azithromycin, corticosteroids, IL-6 antagonists) [136,137]. Developing an effective COVID-19 vaccine is currently the world's leading research priority [138]. Some vaccines have already been approved by the regulatory authorities for the prevention of COVID-19 [139–141].

8.1. Public health and preventive measures

Public health and preventive approaches are the current strategies to curb the transmission of COVID-19 and focus on testing, case tracing, isolation, social distancing, and personal hygiene [142]. Important COVID-19 prevention and control measures in the community include hand hygiene, personal protective equipment (PPE), crowd avoidance, social distancing, isolation, school measures/closures, workplace measures/closures, quarantine, and travel restrictions [143,144].

A study conducted in Singapore recommended closing schools, maintaining effective social distancing in the workplace, and adopting quarantine measures to contain the pandemic once community transmission had been established [145]. Such measures were also found to reduce infection, mortality, and intensive care unit (ICU) admissions [58,146,147]. Social distancing reduces interactions between people and is effective in preventing community transmission [142]. The use of face masks is strongly indicated to reduce COVID-19 transmission in potentially asymptomatic or pre-symptomatic people [148,149]. The widespread use of face masks has been found to be effective in preventing SARS-CoV-2 transmission in highly affected areas in Italy and New York City [150]. Studies have demonstrated that a surgical mask could reduce virus exposure by an average of six times (range: 1.1 to 55 times) and should be worn by the potentially infected subject [151]. The WHO recommended the use of PPE by health care workers as they are more likely to be increasingly exposed to the virus and should wear medical/surgical masks, gowns, gloves, and face shields when treating infected patients or collecting samples [152].

Quarantine was found to be the most effective method for reducing the number of infected cases and decreasing

Table 2. Effect of COVID-19 on different pathophysiological conditions.

Sources	Pathophysiology	Pathogenesis of COVID-19
Xu et al (2020) [113] Gąsecka et al. (2020) [114]	Respiratory diseases	• Endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion capacity are characteristic features of COVID-19 in the respiratory system. • *Early stage* of SARS-CoV-2 infection targets the nasal and bronchial epithelial cells and pneumocytes. • *Later stage* of infection SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating inflammatory response and triggering an influx of monocytes and neutrophils [Ref]. • In *severe condition*, fulminant activation of coagulation and consumption of clotting factors occur indicated as diffuse intravascular coagulation.
Qian et al (2020) [115]	Renal diseases	• Acute kidney injury (AKI) induced by COVID-19 significantly increases the mortality rate. • Detecting proteins and/or blood in urine labs is an early sign of kidney involvement in people with confirmed COVID-19. • The virus shares the same functional receptor, ACE2 present in kidneys, mainly present in proximal tubules, afferent arterioles, collecting ducts, and the thick ascending limb of Helen. • The SARS-CoV-2 induce acute tubular necrosis by infecting kidney tubules directly. • The virus particles can directly infect the cytoplasm of renal proximal tubular epithelium and podocytes, which may induce AKI in COVID-19 patients.
Lippi et al (2020) [116]	Hypertension	• Patients with hypertension have been found to be 2.5 times more likely to develop severe COVID-19. • ACE inhibitors and ARBs are found to increase ACE2; as a result, increased soluble ACE2 in the circulation increase the binding of SARS-Cov-2 to the organ and its pathophysiological effects leading to greater injury.
Gamble et al (2020) [117] Fang et al (2020) [118]	Diabetes Mellitus	• Poor glycemic control is a significant contributor to COVID-19 severity. Impaired neutrophil chemotaxis and phagocytosis in diabetes predisposes to infections in general. • Hyperglycemic events can lead to diabetes ketoacidosis, that interferes with the immune response to mitigate sepsis and recovery.
Tham et al (2019) [119] Memtsoudis et al (2020) [120] Antonia et al (2020) [121]	Obesity	• Obesity is related to a proinflammatory state that potentially predisposes patients to lung injury. • As adipose tissue grows, it can receive a reduced blood supply and thus be subject to hypoxia, necrosis and subsequent inflammation. • Inflamed adipose tissue, and visceral adiposity, secrete more adipokines such as leptin, resistin, retinol binding protein-4, and visfatin, as well as less adiponectin; these contribute to elevated, systemic levels of pro-inflammatory cytokines.
Vepa et al (2020) [122]	Ethnicity	• Asians and Blacks ethnic minority are more predisposed to dyslipidaemia and hypertension, both of which are key cardiovascular risk factors, associated with chronic inflammation, more likely to develop severe COVID-19.
Jin et al (2020) [109]	Gender	• Incidence among males and females was same; however, severe outcomes were more commonly reported among males. • Men with COVID-19 infection are more at risk for worse outcomes and death, independent of age.
Rahman et al (2020) [123]	Age	• Reported severe outcomes increased with age e.g hospitalizations, ICU admissions. • Deaths were highest among persons aged ≥70 years, regardless of underlying conditions, and lowest among those aged ≤19 years.
Gérard et al (2020) [124]	Blood group	• People with type A blood group have higher risk of contracting COVID-19 and of developing severe symptoms than that of type O blood group population.

mortality rates [22,153,154]. A review of 29 COVID-19 related studies found that quarantine can decrease the rate of infected cases (from 81% to 44%) and mortality (from 61% to 31%) [155]. Travel restrictions and lockdown in the early phase of the pandemic in Australia [156] and China [157] helped to decrease transmission effectively. Testing, isolation, and contact tracing were found to be effective in controlling the spread of the virus in countries such as South Korea, Singapore, Taiwan, and Hong Kong [158–161]. In contrast, Italy witnessed a wider outbreak as the country failed to employ such preventive measures during the early phase of the pandemic [161].

8.2. Management strategies based on symptoms

Management strategies of COVID-19 patients depend on the severity of the symptoms of the patients [162,163]:

(1) Mild cases:

- SpO_2 levels of 94%–97% in room air
- Home isolation
  - Symptomatic treatment
- Hospital admission if condition deteriorates
  - O_2 therapy via nasal canula

(2) Moderate cases:

- SpO_2 levels of 90%–94% in room air
- Hospital admission
  - O_2 therapy via nasal canula
  - High-flow nasal oxygen (HFNO) therapy or noninvasive ventilation (NIV) in case of no improvement

(3) Severe cases:

- SpO_2 levels ≤ 90% in room air or patients with ARDS
- Hospital admission
  - O_2 therapy via HFNO/NIV with helmet

Table 3. Viral test for COVID-19.

Sources	Technology	Molecule Tested	Sample Site	Time to Get results	Principle	Advantages	Limitations	Specificity/ Sensitivity
Alcoba-Florez et al (2020) [131]	Real-Time PCR(RT-PCR)	Viral RNA	Nasopharyngeal swab, sputum, stool	3–4 hrs	Nucleic acid amplification test	- Gold standard diagnostic test. - Identifies directly the presence of virus.	Sensitive to sample collection error. Labor intensive. Specialized high-cost equipment.	>97%/ >95%
Peto et al (2020) [132]	LAMP	Viral RNA	Nasopharyngeal swab, sputum, stool	2–3 hrs	Nucleic acid amplification test	- Cost-efficient. - Can be read by eye.	New techniques still under clinical investigation	>95%
Lisboa et al (2020) [133]	ELISA	IgG or IgM	Blood	1–3 hrs	Detection of IgM/IgG ot RBD IgG antibodies, via colorimetric assay	- Cost-effective. - Well documented in science. - Test 96 samples at a time.	Requires laboratory. Not well- established for SARS-CoV-2	79%/80%
Nicol et al (2020) [134]	Lateral Flow Immunoassays	IgG or IgM	Blood	15 to 20 min	Detection of IgM/IgG antibodies via color change of strip in lateral flow assay	- Extremely quick results. - Little training required.	- Evidence for accuracy still under investigation. - Expensive. - Not effective for large batch testing	96%/80%

- Transfer to ICU
  - Invasive ventilation via endotracheal intubation for patients with ARDS in cases of falling SpO_2 levels
- ARDS management

8.3. Pharmacological treatments

8.3.1. Antiviral agents

Extensive research is ongoing regarding antiviral therapies for the treatment of COVID-19. Although several antiviral therapies are being investigated by scientists, no treatments have been shown to be effective in treating COVID-19 [164,165]. Preliminary results are available from The Adaptive COVID-19 Treatment Trial (ACTT-1) from hospitalized COVID-19 patients. This double-blind randomized control trial (RCT) conducted in 60 trial sites and 13 subsites (United States of America [USA] (45 sites), Denmark (8), UK (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1)] showed that remdesivir was associated with a shorter median recovery time compared with placebo (11 vs. 15 days) with evidence of lower respiratory tract infection [165]. The trial also showed a significant mortality benefit (remdesivir group 4.0% vs. control group 12.7%). A study conducted in China, prematurely terminated due to adverse events of remdesivir, found that COVID-19 patients, with symptom duration of ≤ 10 days, improved faster compared to that of the placebo group, but this finding was not statistically significant [166]. A study conducted in the USA, Europe, and Canada showed clinical improvement among severe COVID-19 hospitalized patients (36 of 53 patients; 68%) who were treated with compassionate use of remdesivir [167]. Another RCT that included 584 patients with moderate COVID-19 at 105 hospitals in the United States, Europe, and Asia found those who took a 5-day course of remdesivir compared with those randomized to standard care had a statistically better outcome [168]. However, the WHO Solidarity Trial [169], conducted in 30 countries, found that remdesivir (including hydroxychloroquine, lopinavir/ritonavir, and interferon) had little or no effect on overall mortality, ventilation need, and duration of hospital stay.

Although the preliminary findings of the ACTT-1 study supported the use of remdesivir, the researcher recommended that remdesivir or any other antiviral drug alone is not effective, as the mortality rate is higher with the use of remdesivir. Another randomized, controlled, open-label trial with lopinavir/ritonavir treatment demonstrated no benefit compared to standard care [170]. Similarly, the UK RECOVERY (Randomized Evaluation of COVID-19 therapy) reported no benefit of lopinavir/ritonavir on survival, the clinical course, or the length of hospital stay [171]. After interim analysis of the trial results, the WHO SOLIDARITY and UK RECOVERY trials discontinued the lopinavir/ritonavir arms as the trials produced little or no reduction in the mortality of hospitalized COVID-19 patients in comparison to the standard of care [172,173]. Remdesivir received conditional marketing authorization by the European Commission on 3 July 2020, to treat COVID-19 patients [174]. Several anti-flu drugs, such as oseltamivir [175] and arbidol [176], have been used to treat COVID-19 patients and demonstrated a certain efficacy. Although the WHO recommended against the use of remdesivir in COVID-19 patients [177], the U.S. Food and Drug Administration (FDA) approved remdesivir on 22 October 2020, for the treatment of COVID-19 patients requiring hospitalization [178]. Remdesivir (Veklury) was the first drug approved by the FDA and indicated 'for the treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg' [178].

8.3.2. Corticosteroids

Corticosteroids have received considerable attention for the treatment of COVID-19 [179,180] and were found to be beneficial in several COVID-19-related conditions such as sepsis, pneumonia, and ARDS [181–183]. The RECOVERY trial found that dexamethasone reduced mortality by one-third in critically ill COVID-19 patients [184,185]. The medication was most helpful for patients on a ventilator or those who needed extra oxygen, but no benefit was noted for those with less severe symptoms. However, other studies reported conflicting results, with some showing benefits [186–188], while others demonstrated potential harm [189,190]. A meta-analysis of 15 studies [191] identified an increased risk of mortality and multi-organ dysfunction, no mortality benefit, and possibly an increased risk of death with the use of corticosteroids among COVID-19, SARS, and MERS patients. A recent WHO report suggested that systemic corticosteroids likely reduced 28-day mortality in patients with critical COVID-19 but may have increased the risk of death in non-severe patients [174]. The report recommended the use of systemic corticosteroid therapy for 7 to 10 days in patients with severe and critical COVID-19 and no corticosteroid treatment for non-severe patients in whom it may cause harm.

8.3.3. Antiviral/immunomodulatory drugs

Chloroquine and hydroxychloroquine are usually used as immunomodulatory therapies. Both drugs are approved by the FDA for the treatment or prevention of malaria. Recently, the FDA has approved the use of chloroquine and hydroxychloroquine to treat COVID-19 patients 'only in hospitalized patients with COVID-19 when clinical trials are not available, or participation is not feasible, through an Emergency Use Authorization (EUA)' [192]. According to ClinicalTrials.gov, 212 hydroxychloroquine trials (179 randomized) and 38 chloroquine trials (31 randomized trials) were registered until 3 September 2020 [193].

However, the outcomes of treatment with chloroquine (500 mg every 12 h) and hydroxychloroquine are not encouraging. The RECOVERY trial found that hydroxychloroquine did not reduce 28-day mortality when compared to the usual standard of care. In addition, patients who received hydroxychloroquine had a longer median hospital stay and increased risk of progressing to invasive mechanical ventilation or death than those who received the standard of care [194]. In a multicenter, randomized, open-label, three-group, controlled trial involving hospitalized patients in Brazil, no positive outcomes were reported with hydroxychloroquine alone or with hydroxychloroquine plus azithromycin among hospitalized patients with mild to moderate COVID-19 [195]. The

occurrence of an adverse event (e.g. elevation of liver enzyme levels, and prolongation of the QTc interval) was more frequent among patients who received hydroxychloroquine or hydroxychloroquine plus azithromycin than among those who did not receive either agent [195]. Another open-label, randomized clinical trial at 57 centers in Brazil involving hospitalized patients with severe COVID-19 also failed to show the effectiveness of hydroxychloroquine plus azithromycin over hydroxychloroquine alone [196]. Large retrospective observational studies in hospitalized patients suffering from COVID-19 also showed no evidence of benefit for hydroxychloroquine with or without azithromycin [197,198]. However, a large, multicenter, retrospective, observational study in the USA reported that treatment with hydroxychloroquine alone and in combination with azithromycin reduced COVID-19 associated mortality [199]. Several randomized trials conducted among non-hospitalized patients with COVID-19 failed to demonstrate a clinical benefit of hydroxychloroquine treatment [200,201].

The COVID-19 Treatment Guidelines of National Institutes of Health, USA recommends against the use of high-dose chloroquine to treat COVID-19 due to severe toxicities, such as higher rates of mortality and QTc prolongation [202,203]. It has been warned that the combination of hydroxychloroquine and azithromycin should be used with caution as the combination is associated with QTc prolongation in patients with COVID-19 [204].

8.3.4. Immune-based therapy

The agents that modulate the immune response are used for the management of moderate to critical COVID-19, including human blood-derived products and immunomodulatory therapies. Human blood-derived products are collected from patients who have recovered from COVID-19 infection (e.g. convalescent plasma and immunoglobulin products) [205,206]. Other agents approved to treat other immune and/or inflammatory syndromes are also considered to treat COVID-19 patients, including corticosteroids (e.g. glucocorticoids) [207], interleukin inhibitors [208,209], interferons [210], and kinase inhibitors [211].

It has been suggested that convalescent plasma may help suppress the virus and modify the inflammatory response [205]. At present, there is limited evidence from clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19 [212]. A retrospective evaluation conducted by the FDA and the Mayo Clinic (USA) in >70,000 patients who received COVID-19 convalescent plasma demonstrated that plasma with high antibody titers may be more effective than low-titer plasma in non-intubated patients [213,214]. The FDA also evaluated 20,000 hospitalized patients with COVID-19 convalescent plasma and reported that transfusion is safe in patients with COVID-19 and found low overall rates of serious adverse events (SAEs) [215]. It is important to note that the FDA approved EUA on 23 August 2020, to use convalescent plasma in hospitalized patients with COVID-19 [216].

Interferon β was found to be effective against coronaviruses [217]. The WHO Solidarity Trial [169] found that interferon had little or no effect on overall mortality, ventilation need, and duration of hospital stay. However, a randomized, double-blind, placebo-controlled phase 2 trial conducted in the UK [218] demonstrated that hospitalized patients infected with SARS-CoV-2 received inhaled nebulized interferon β-1a had significantly greater odds of clinical improvement and rapid recovery on the WHO ordinal scale for clinical improvement [219]. Further studies should be conducted to evaluate the effectiveness of high-risk COVID-19 populations such as elderly, comorbid, or immunosuppressed patients [169,218].

8.3.5. Adjunctive therapy

Adjunctive therapies are used in patients with COVID-19, and some clinical trials are ongoing to identify the effects of these agents [202]. It was observed that COVID-19 patients were associated with a prothrombotic state and had a higher inci-

Table 4. COVID-19 vaccine candidates in phase III trials [231,235].

10 candidate vaccines	Vaccine platform	Antigen**	Location of phase III studies
Sinovac	Inactivated virus	S	Brazil
Wuhan Institute of Biological Products/ Sinopharm	Inactivated virus	S	United Arab Emirates
Beijing Institute of Biological Products/ Sinopharm	Inactivated virus	S	China
University of Oxford/ AstraZeneca	Viral vector*	S	USA
CanSino Biological Inc./ Beijing Institute of Biotechnology	Viral vector*	S	Pakistan
Gamaleya Research Institute	Viral vector	S	Russia
Janssen Pharmaceutical Companies	Viral vector	S	USA, Brazil, Colombia, Peru, Mexico, Philippines, South Africa
Novavax	Protein subunit	S	UK
Moderna/NIAID	RNA	S	USA
BioNTech/Fosun Pharma/Pfizer	RNA	S	USA, Argentina, Brazil

* Single dose schedule. ** S – Spike protein

Table 5. Vaccines found to be effective in preventing COVID-19 [139,141,237,238].

Company	Type of vaccine	Doses	Route*	Effectiveness	Storage
Oxford University-AstraZeneca	Viral vector (genetically modified virus)	2	IM	62–90%	Regular fridge temperature
Pfizer/BioNTech	RNA	2	IM	95%	−70°C
Moderna	RNA (Part of virus genetic code)	2	IM	95%	−20°C up to 6 months
Gamaleya (**Sputnik V**)	Viral vector	2	IM	92%	Regular fridge temperature

*Intra-muscular

dence of venous thromboembolism [220,221]. A French prospective multicenter study among ICU patients (n = 150) demonstrated that 16.7% of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications despite prophylactic anticoagulation [221]. Another study conducted in the Netherlands found a 31% incidence of thrombotic complications in critically ill ICU patients with COVID-19 (n = 184) [222]. Therefore, patients with COVID-19 admitted to the ICU should receive pharmacological thrombosis prophylaxis [222].

Vitamin and mineral supplements are typically used to treat respiratory viral infections. Several studies have examined the effectiveness of vitamin and mineral supplements for the treatment and prevention of SARS-CoV-2 infection. High doses of vitamin C are recommended for the treatment of sepsis [223] and ARDS in patients with serious COVID-19. Several recent studies have examined the impact of vitamin D on COVID-19. One study of 489 people found that those who had a deficient vitamin D status were 1.77 times more likely to be infected with the virus than people with normal vitamin D status [224]. Despite the lack of evidence of whether vitamin D treatment may decrease the incidence of COVID-19, the use of vitamin D treatment is advocated due to its low risk and low cost [225,226]. Some clinical trials are ongoing with zinc supplementation alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19 [227–230]. A single-institution retrospective study in the USA showed 'a lack of a causal association between zinc and survival in hospitalized patients with COVID-19' [231].

8.4. A vaccine

Scientists are conducting research on the development of COVID-19 vaccines. At present, there are >100 COVID-19 vaccine candidates under development, some of which are in the human trial phase [138]. The WHO is working through the Access to COVID-19 Tools (ACT) accelerator to speed up the pandemic response and distribute vaccines via the COVID-19 Vaccines Global Access (COVAX) [led by WHO, Global Alliance for Vaccines and Immunization (GAVI) and Coalition for Epidemic Preparedness Innovations (CEPI)] to facilitate equitable access and distribution [138]. The WHO announced the launch of the WHO COVID-19 Solidarity vaccine trial on 28 May 2020, which is an international, randomized controlled phase III trial of different vaccine candidates [232]. It is one of the largest trials that enrolled almost 280,000 patients from 470 hospital sites in over 34 countries [232,233]. The trial aims to examine the efficacy of multiple vaccines (within a short period of vaccine introduction into the study), so that weakly effective vaccines are not deployed to treat patients with COVID-19 [232–235].

Until October 2020, there were 42 COVID-19 candidate vaccines in the clinical evaluation, of which 10 were in phase 3 trials (Table 4) [232,236]. There are 151 candidate vaccines for preclinical evaluation [232]. So far, four vaccines have been reported to be effective for the prevention of COVID-19: Pfizer/BioNtech, Moderna, Oxford, and Sputnik V vaccines. The details of these vaccines are presented in Table 4 [232,236] and Table 5 [139,141,237,238]. The first two vaccines received emergency approval for use in the prevention of COVID-19 [139–141]. Whether these vaccines are effective against new strains of SARS-CoV-2, which were recently identified in the UK and other countries, needs further investigation.

8.4.1. Pfizer/biontech vaccine

On 9 November 2020, Pfizer and its German partner BioNTech announced that their experimental vaccine was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection, based on initial data from Phase 3 trials [239]. According to Pfizer, the vaccine prevented COVID-19 symptoms in 90% of 94 patients who received the vaccine compared to the placebo. As of 8 November 2020, a total of 38,955 participants had received a second dose of the vaccine, of which 42% of global participants and 30% of U.S. participants had diverse racial and ethnic backgrounds [239]. Approximately 21% of the participants had at least one underlying comorbidity, that is, obesity, diabetes, or pulmonary disease [240]. On 16 November 2020, Pfizer released updated information concerning the observed efficacy of its vaccine in adults over 65 years of age, which was more than 94% [241]. On 11 December 2020, the FDA authorized the Pfizer/BioNTech vaccine for emergency use for individuals aged 16 years and older in the USA. This is the first COVID-19 vaccine approved by the FDA [139]. The European Medicines Agency (EMA) has also approved the Pfizer-BioNTech vaccine as the first COVID-19 vaccine to be used in EU countries [140].

The Pfizer/BioNTech vaccine is a messenger RNA (mRNA) vaccine, also known as BNT162b2, based on the SARS-CoV-2 S glycoprotein antigen and formulated in lipid nanoparticles (LNPs) [240]. It is a highly purified single-stranded, 5′-capped mRNA produced by cell-free *in vitro* transcription from the corresponding DNA templates [242]. Its mechanism of action consists of nucleoside-modified mRNA (modRNA) encoding the viral S glycoprotein of SARS-CoV-2, which is formulated in lipid particles. This allows the delivery of RNA into host immune cells to enable the expression of the SARS-CoV-2 S antigen.

8.4.2. Moderna vaccine

On 16 November 2020, Moderna, Inc., a US pharmaceutical company, announced that its vaccine was 94.5% effective (Phase 3 COVE study) at preventing COVID-19 related illness, including severe cases, and is generally well tolerated [243]. An interim analysis of 95 cases (90 COVID-19 in the placebo group versus 5 cases in the mRNA-1273 group) demonstrated 'a point estimate of vaccine efficacy of 94.5% ($p < 0.0001$)' [243]. The Coronavirus Efficacy and Safety (COVE) trial, a randomized and placebo-controlled study, recruited 30,000 participants in the USA, aged 18 and above [243]. Unlike the Pfizer vaccine, it can be stored at standard refrigerator temperatures, which are available in doctors' offices, pharmacies, and hospitals [244]. On 18 December 2020, the FDA issued an EUA for the Moderna vaccine for use in individuals 18 years of age and older in the USA [141].

The Moderna vaccine also used a similar technology to Pfizer/BioNTech. The active ingredient of the Moderna vaccine is a synthetic mRNA encoding the pre-fusion stabilized

S glycoprotein of SARS-CoV-2. Both vaccines differ in their composition of LNP that encase the RNA; additionally, the RNA in both vaccines encodes a slightly modified form of the SARS-CoV-2 S protein [245]. Moderna's formulation allows the vaccine to be stored at a higher temperature than Pfizer's, which must be kept at −70°C, much colder than a normal freezer. Moderna's vaccine can be stored in a − 20°C freezer for 6 months, and in a refrigerator (at approximately 4°C) for 30 days [141,237].

8.4.3. Oxford vaccine

Another vaccine developed by the University of Oxford, UK, and another pharmaceutical giant AstraZeneca was found highly effective – two full doses gave 62% protection (n = 8,895), a half dose followed by a full dose 90% (n = 2,741). Overall, the trial showed 70% protection (n = 11,636) [246]. The trial participants (n = 23,000) were from the UK and Brazil. The vaccine is cheaper than Pfizer and Moderna and does not require an ultra-cold storage and transport system [247]. As the vaccine was found to be more effective in trial participants who received a lower dose, AstraZeneca is now planning to run a new global trial [247].

Unlike the mRNA vaccines of Pfizer-BioNTech and Moderna, this vaccine uses double-stranded DNA. The mechanism of the vaccine is based on its effect on the S protein of SARS-CoV-2. The Oxford-AstraZeneca team used a modified version of the cold-causing chimpanzee adenovirus, known as ChAdOx1. Adenovirus derived from chimpanzee with E1 and E3 deletions encoding full-length S protein with a tissue plasminogen activator signal peptide [248]. With the use of genetic engineering methods, a portion of the DNA that is used for viral replication was deleted, so the adenovirus can no longer replicate and cause infection in the human body [249].

8.4.4. Sputnik V vaccine

The Russian vaccine Sputnik V was developed by the Gamaleya Research Institute in coordination with the Russian Defense Ministry. It was administered to 18,794 volunteers who received both the first and second doses of the vaccine or placebo. It showed very high efficacy; higher than 95% [238]. It is an adenovirus vector-based vaccine that uses a two-shot model with two different human adenoviral vectors, Ad5 and Ad26, for each shot [250]. When the first vaccine containing the vector with the S protein of SARS-CoV-2 is introduced into the human body, it synthesizes the S protein and initiates an immune response. After 21 days, the booster dose of the vaccine, based on another adenovirus vector unknown to the host cell, is administered. The body reacts by generating a further immune response that provides longlasting immunity [251].

9. The ethics of epidemics: ethical and moral issues associated with COVID-19

When it comes to global pandemics such as COVID-19, there are numerous issues in medical ethics that must be addressed and adhered to in order to ameliorate the human condition [252,253]. One of the most important issues to consider is patient confidentiality [254]. While confidentiality must be maintained between physicians and patients during standard medical care, when it comes to the treatment of a patient diagnosed with COVID-19, an exception has to be made. Since COVID-19 is considered a reportable illness, the type of illness that poses a threat to another person, doctors must follow Tarasoff's Law of duty to warn and protect [255]. In other words, physicians are required to report quarantine and follow-up contact tracing [256].

Another ethical issue, autonomy, must be considered when a patient is diagnosed with COVID-19. A legally competent adult patient (18 years of age and older) may exercise their autonomous right to refuse treatment [257]. In such a case, a physician's duty is to notify the patient about the possible health outcomes of refusing the treatment. However, COVID-19 is considered to be a quarantinable disease; thus, physicians could detain infected individuals during the infectious period.

In addition, informed consent is not required in the case of an emergency, such as in the case of a life-saving procedure for a patient diagnosed with COVID-19. Another example of an exception to obtaining informed consent is when the COVID-19 patient waived his or her right receiving information related to COVID-19 [254]. If a physician has to treat a patient diagnosed with COVID-19 who is incapacitated because he or she is either psychotic, unconscious, suicidal/homicidal, or under the influence, obtaining informed consent is not necessary [257]. Furthermore, physicians can invoke therapeutic privilege if physicians agree that the COVID-19 patient is unable to make good decisions for himself or herself. In this case, beneficence trumps the adult patient's autonomy; hence, informed consent is not required during treatment [255].

In the case of minor health care (persons younger than 18 years of age), legally competent adult caregivers give consent for treatment [256]. Thus, when it comes to treating a minor diagnosed with COVID-19, the same rule applies as in the case of an adult patient. While physicians must always obtain informed consent from legal guardians when treating a minor, lifesaving treatment is always an exception [234]. Hence, legally competent adult guardians cannot refuse the lifesaving treatment of COVID-19 minors. On the other hand, when it comes to legally competent emancipated minors who are diagnosed with COVID-19, the physician must apply Tarasoff's Law of duty to warn and protect [256]. In other words, the physicians must report, and quarantine emancipated minors diagnosed with COVID-19 since they pose a threat to another person and community. Furthermore, physicians could override their autonomous rights to refuse therapy by invoking therapeutic privileges, just in the case of adult patients [257].

10. Conclusion

The COVID-19 pandemic is the greatest global public health crisis since the pandemic influenza outbreak of 1918. Since its origin in Wuhan, the COVID-19 pandemic has now spread around the world, causing significant morbidity and mortality. Direct person-to-person respiratory transmission has rapidly amplified the spread of the virus, making it difficult to contain

its spread within the community. Moreover, some patients are completely asymptomatic with a mild influenza-like illness and a positive swab test, and some present with serious symptoms that require immediate hospitalization. Currently, there is no effective antibody test available, and an effective, rapid, and sensitive serological test for COVID-19 is urgently needed for rapid diagnosis. Moreover, there is no effective approved therapy for COVID-19. Personal hygiene is fundamental for preventing transmission. Current treatment and management are mainly supportive of oxygen therapy, antivirals, steroids, hydroxychloroquine, immunomodulators, and plasma exchange therapy. We need to keep a close eye on human clinical trials for optimistic news on vaccine development.

10.1. Limitations

The information presented in this review paper must be considered in the context of potential limitations. There has been an overwhelming amount of information published since the outbreak of COVID-19, and most of the journal papers published, mainly in the early phase of pandemics, were not based on clinical/scientific research. The evidence-based information garnered for this review was obtained after careful review of currently published journal papers, reports, policy guidelines.

Another drawback of this paper is its narrative nature, which may limit the critical analysis of the information. A systematic review using appropriate protocols [258] of the current literature would help to draw reliable and accurate scientific information, improve the generalizability and consistency of findings, and increase the precision of the conclusion presented to formulate policy guidelines. However, the present review covers the most updated information on the anniversary of the COVID-19 pandemic, and such documentation is necessary for keeping readers, researchers, scientists, and policymakers appraised of the current status of the pandemic [259].

11. Expert Opinion

The COVID-19 pandemic has created a public health crisis, taking an enormous toll on humanity, disrupting lives and livelihoods [4,77,259]. The scale and severity of COVID-19 is unprecedented, and millions of people have been infected with large numbers of morbidities and mortalities [4,57]. Genetic sequencing suggests that the virus belongs to the family Coronaviridae and genus Betacoronavirus, which is closely linked to the SARS virus [27–30]. Epidemiological and virologic studies have reported that COVID-19 usually transmits from person to person through several routes, mainly via respiratory droplets [260–263]. Evidence of virological assessment of transmission of infection from people with presymptomatic stage is limited due to the lower number of samples collected [264,265]. Some infected persons can be contagious during the presymptomatic phase, from to 1–3 days before symptom onset [266,267]. For individuals, transmission risk is found to be greatest on the day of symptom onset in symptomatic patients [264,265,268,269]. Ferretti et al. analyzed five datasets and demonstrated that approximately 10% of transmissions may occur two days before the manifestation of symptoms [270]. Another review identified that 31% of infected individuals remain asymptomatic [271].

While most people with COVID-19 show only mild (40%) or moderate (40%) symptoms, approximately 15% of patients exhibit severe symptoms (requiring oxygen therapy), and 5% develop critical disease with complications (e.g. respiratory failure, ARDS, sepsis, septic shock) [135]. The WHO reported that the crude mortality ratio (the number of reported deaths divided by the reported cases) is 3–4%; however, the true mortality of COVID-19 will take some time to determine [271]. Elderly people, smokers, and patients with comorbid diseases (such as diabetes, hypertension, cardiac disease, chronic lung disease, and cancer) have an increased risk of severe disease and death [272,273].

The host response to SARS-CoV-2 is a key factor in the presentation of disease severity; however, variations in viral strain phenotypes, specifically those associated with the glycoprotein components of the virus, have contributed to the efficient transmission of the virus during the current pandemic [274].

Although the sequence diversity of SARS-CoV-2 is low, its global spread has resulted in several thousand viral variants due to mutations in the native strain over time [259,275]. The most notable of these, as first documented by Korber *et al*. [277], is a viral variant with an amino acid substitution in the S glycoprotein spike. The mutation, which causes a substitution of the amino acid aspartate (D-biochemical symbol), at the 614th amino acid position of the spike protein with glycine (G), has overtaken the native SARS-CoV-2 virus as the most prevalent infective strain [277]. This variant, termed D614G, is associated with increased transmissibility and higher viral loads in COVID-19 patients, has not been demonstrated to cause an increase in disease severity [276,278]. The substitution enhances viral replication within the respiratory tract of infected individuals and affects neutralization susceptibility [274].

Compared with other highly mutable viruses, such as HIV, SARS-CoV-2 has a low mutation rate; however, as pandemics progress, it is possible that antigenic drift events, which slowly accumulate mutations over time, can lead to increased fitness as well as immunological and drug resistance [279]. This is a key consideration for current and future vaccine development.

Case detection, contact tracing, surveillance, infection prevention and control, physical distancing, and clinical management are effective strategies used to contain COVID-19 cases [280,281]. Early detection and reporting can prove to be useful, and contact tracing is a widely used surveillance system to fight the ongoing epidemic of COVID-19 [282]. Contact tracing provides information that also helps to better understand the transmission and epidemiology of COVID-19 [158,281]. Moreover, some countries are now experiencing the 'second' or 'third' waves of coronaviruses [283]. Scientists have proposed using app-based contact tracing to keep the epidemic in control as an alternative [284]. A digital technological system, called 'proximity tracking ' is now a widely used surveillance system for COVID-19 [285].

Currently, PCR, the gold standard for detecting SARS-CoV-2, is used to detect the virus in specialized laboratories [2,125,127,286]. The test has high sensitivity and specificity for the detection of viral ribonucleic acid (RNA) [2,286]. The high volume of samples could lead to a shortage of reagents and may increase the turn-around time of the tests. Alternatively, rapid

antigen tests provide multiple benefits, including ease of use, quick results (10 to 30 minutes), low cost, and can be performed both in the laboratory and at the point of patient care [280]. Although rapid antigen testing has a lower sensitivity, the WHO recommends the use of this test where PCR is unavailable or where reduced turnaround-time is clinically necessary [287]. Antigen tests are immunoassays that are used to determine if the person has an active disease [288], whereas a positive antibody test indicates that the patient is likely infected with COVID-19 at some time in the past [289]. Antibody tests can be conducted in laboratory settings (e.g. enzyme-linked immunosorbent assays, chemiluminescence immunoassays) or point of care (e.g. Abbott SARS-CoV-2 assay, Roche Elecsys assay) [290].

To date, no effective specific drug therapy or vaccine has been found to limit the spread of this pathogen. Infection prevention and control measures, supportive needs, and intensive care support are the main strategies for clinical management of COVID-19 infection [136]. General prevention and protection measures regarding the containment and management of the second or third waves are necessary to minimize the risk of infection. There is some promising news regarding COVID-19 vaccines. Several phase 3 clinical trials are in progress or are being planned in some countries. As of 24 November 2020, four vaccines were reported to be 62–95% effective (Table 5) [139,141,237,238]. These promising results have fueled optimism around the world, as we may be a step closer to defeating this deadly virus. Certainly, there is light at the end of the tunnel. Equitable access and effective distribution of these vaccines in all countries will save millions of lives.

ABBREVIATIONS

COVID-19 -	Coronavirus disease 2019
SARS-CoV-2 -	Severe acute respiratory syndrome coronavirus-2
WHO -	World Health Organization
CVD -	Cardiovascular diseases
UTI -	Upper respiratory tract infections
HCoV -	Human coronavirus
SARS -	Severe acute respiratory syndrome coronavirus
MERS -	Middle East Respiratory Syndrome
ACE2 -	Angiotensin-converting enzyme 2
RBD -	Receptor-binding domain
NTD -	N-terminal domain
R_0 -	Reproduction number
ARDS -	Acute respiratory distress syndrome
PRRs -	Pattern recognition receptors
TLRs -	Toll-Like Receptors
CRP -	C-Reactive Protein
MODS -	Multiple organ dysfunction syndrome
CDCs -	Centres for Disease Control and Prevention
PCR -	Polymerase Chain Reaction
LAMP -	Loop-mediated isothermal amplification
EAU -	Emergency Use Authorization
ELISA -	Enzyme-Linked Immunosorbent Assay

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