

Review

Overview of COVID-19 Disease: Virology, Epidemiology, Prevention Diagnosis, Treatment, and Vaccines

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Abstract: Coronaviruses belong to the “Coronaviridae family”, which causes various diseases, from the common cold to SARS and MERS. The coronavirus is naturally prevalent in mammals and birds. So far, six human-transmitted coronaviruses have been discovered. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan, China. Common symptoms include fever, dry cough, and fatigue, but in acute cases, the disease can lead to severe shortness of breath, hypoxia, and death. According to the World Health Organization (WHO), the three main transmission routes, such as droplet and contact routes, airborne transmission and fecal and oral for COVID-19, have been identified. So far, no definitive curative treatment has been discovered for COVID-19, and the available treatments are only to reduce the complications of the disease. According to the World Health Organization, preventive measures at the public health level such as quarantine of the infected person, identification and monitoring of contacts, disinfection of the environment, and personal protective equipment can significantly prevent the outbreak COVID-19. Currently, based on the urgent needs of the community to control this pandemic, the BNT162b2 (Pfizer), mRNA-1273 (Moderna), CoronaVac (Sinovac), Sputnik V (Gamaleya Research Institute, Acellena Contract Drug Research, and Development), BBIBP-CorV (Sinofarm), and AZD1222 (The University of Oxford; AstraZeneca) vaccines have received emergency vaccination licenses from health organizations in vaccine-producing countries. Vasso Apostolopoulos, Majid Hassanzadeganroudsari

Keywords: coronavirus; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); vaccines



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1. Introduction

Small parasitic particles that are unable to reproduce on their own are called viruses. If they enter the host cell, they can infect the host cell and replicate. Genetic material (DNA or RNA strand structure), a capsid protein coat (protection of genetic material), and an outer sheath of lipids are the known components of a virus structure. The fundamental particle of an infectious virus composed of nucleic acid and an external protein shell is called a virion [1]. In the modern world, a record for detecting respiratory infections caused by the virus in children and adults date back to the 1960s [2]. One of the essential viruses available that cause respiratory syndromes are coronaviruses. This family

is called Coronaviridae. Many people are exposed to the coronavirus once in their life-time, which often causes diseases such as pneumonia or bronchitis. Coronaviruses are single-stranded, enveloped RNA viruses with a 120–80 nm diameter and are divided into four groups: Alpha coronaviruses, Beta coronaviruses, Gamma coronaviruses, and Delta coronaviruses [3,4]. The four types of coronavirus, HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoVHKU1 are less pathogenic and cause only mild respiratory illness [5]. Nevertheless, two types of coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), caused two deadly epidemics [6]. In 2003, due to the SARS-CoV emergency in southern China and its widespread prevalence, extensive research was conducted to control and treat the disease. According to the World Health Organization, more than 8000 people were infected, and 774 deaths were reported [7]. In addition, in 2012, another outbreak of the acute respiratory disease was reported in Saudi Arabia where MERS-CoV was identified as the cause of the epidemic. According to published reports, the mortality rate was over 35% [8]. It was stated that market civets and dromedary camels were the primary sources of SARS-CoV transmission and MERS-CoV transmission to humans [6]. The known animal origins of coronaviruses are demonstrated in Figure 1.

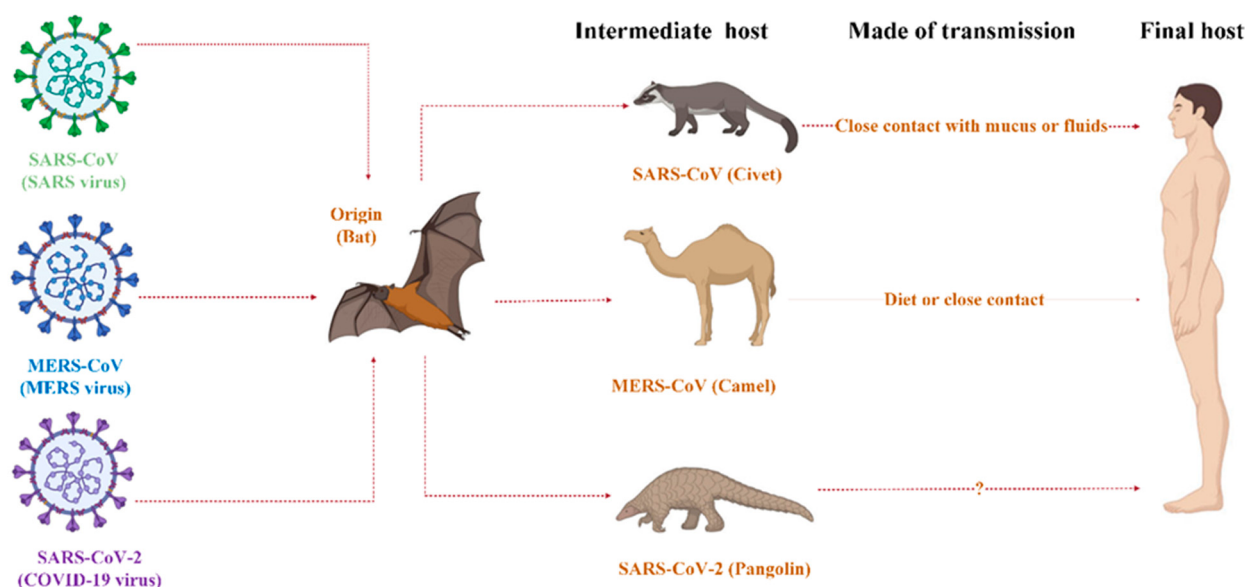


Figure 1. Animal origins of human coronaviruses (Created with [BioRender.com](https://www.biorender.com), accessed on 1 August 2020).

On 11 March 2020—The World Health Organization (WHO) declared COVID-19 as a pandemic caused by SARS-CoV-2 [9]. The main effect of SARS-CoV-2 is in human respiratory system cells. However, new studies have revealed the impact of the virus on the cells of the gastrointestinal tract, kidney system, liver, pancreas, eyes, and brain [10]. The SARS-CoV-2 virus is about 79% and 50%, similar to SARS and MERS viruses, respectively [11]. Widespread prevalence due to the high transmission strength and complexity of COVID-19 treatment compared to SARS-CoV and MERS-CoV has led to a global crisis and preventing the disease's spread is a necessity. This study provides an overview of all aspects of the disease, such as virology, modes of transmission, and diagnosis. New therapeutic guidelines and vaccines approved by the World Health Organization are also mentioned.

2. Virology

Coronaviruses are virions that have viral envelopes. The diameter of these virion particles is 120 nm. Cloverleaf structures such as glycoproteins and proteins on the virus's surface have created a crown-like structure in it. These viruses are also known as coronaviruses because of their crown structure. A section called nucleocapsid is made of capsid-coated proteins in these viruses and is placed inside the virus's genetic material (Figure 2) [12]. The coronavirus has a genomic genus of RNA. This genetic material is seen as a spiral or circular in the nucleocapsid of the virus. The coronavirus genome consists of a single strand of positive RNA (ribonucleic acid). This virus's genomic RNA has a methylated warhead in its 5' region and is rich in adenine nucleotide at the end of its 3'. Coronaviruses encode a protein called the replicase enzyme in their genome, which functions by transcribing the virus genome and producing new copies using the host cell's capabilities [13]. According to studies, SARS-CoV-2 is a beta-corona virus genus member. The SARS-CoV-2 virus is composed of four structural proteins, including nucleocapsid (N), spike (S), membrane (M), and envelope (E) (Figure 2). Protein M plays a vital role in introducing the virus into the body and forming envelopes [14]. Protein E is responsible for the proliferation, germination, envelope formation, and spread of the virus [15]. Increasing transcription and assembly of viruses is the responsibility of multipurpose N protein [16]. In addition, the virus binding to host cells is the responsibility of the Spike (S) protein. Therefore, it has a unique rank in pharmaceutical and vaccine research. It should be noted that, due to the lack of response to neutralizing or immune antibodies, proteins N, M, and E are not considered as drug targets [17].

As depicted in Figure 2, the S glycoprotein of the newly discovered SARS-CoV-2 is composed of two subunits, S1 and S2, and is commonly represented as a sword-like spike. The real structure of this protein, however, can be observed via crystallography. The Protein Data Bank (PDB) model of this glycoprotein reveals how the subunits are comprised of different regions that are fundamental to the infection process. S1 and S2 are linked together by a polybasic amino acid bridge, which may be necessary for studying viral targeting [18]. The virus binds to the host cell with the help of an S-protein and penetrates the cell. After the penetration process, the transcript process begins, and the virus multiplies until the host cell is wholly infected and destroyed [19].

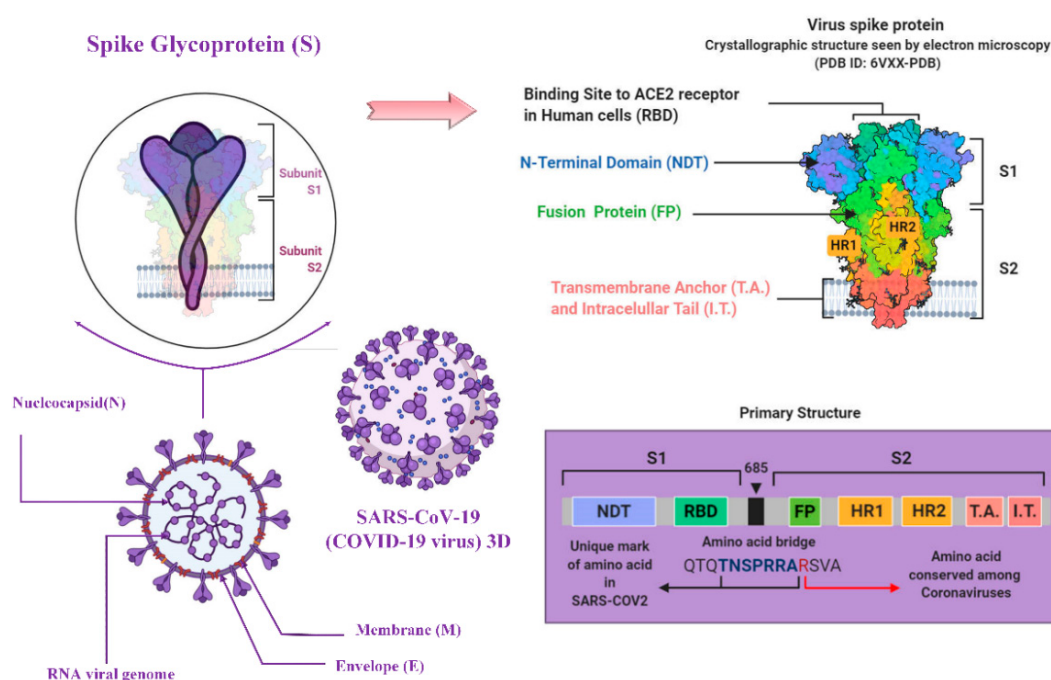


Figure 2. An in-depth look into the SARS-CoV-2 Spike Glycoprotein (Reprinted from “An In-depth Look into the Structure of the SARS-CoV-2 Spike Glycoprotein”, by BioRender.com, accessed on 1 August 2020) [20].

Angiotensin-converting enzyme 2 (ACE2) receptors in mammalian lung cells act as recipients of the S-spike protein, releasing endogenous viral RNA genetic material into host cells (Figure 3).

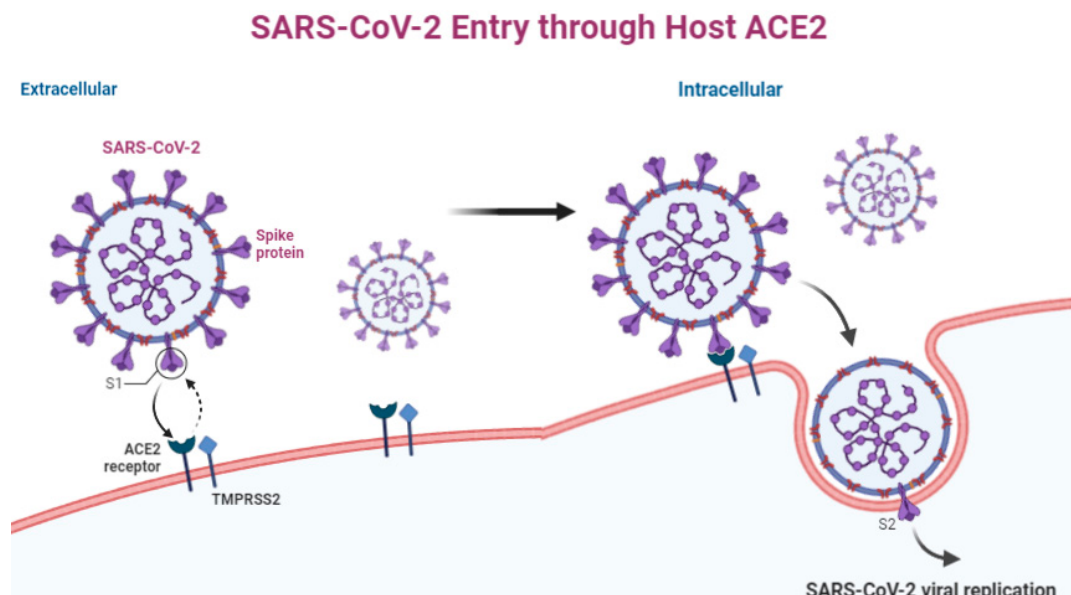


Figure 3. SARS-CoV-2 targeting ACE2 receptor and entry in the infected cell (Adopted from “SARS-CoV-2 Targeting of ACE2 Receptor and Entry in Infected Cell”, by [BioRender.com](https://www.biorender.com), accessed on 1 August 2020) [21].

One of the crucial functions of angiotensin-converting enzymes (ACE2) is to regulate the renin–angiotensin system (RAS). In general, the angiotensin-converting enzyme 2 (ACE2) acts as a cell surface receptor and causes SARS-CoV-2 to enter host cells and plasma and is expressed in organs such as the lungs, kidneys, and heart. Moreover, one of the reasons for the development of COVID-19 is the disturbance of the ACE/ACE2 balance and the activation of RAAS by SARS-CoV-2, especially in patients with underlying cardiovascular disease problems, hypertension, and diabetes [22]. Figure 4 presents the expression of ACE2 Receptor in Human Host Tissues. ACE2 expression in alveolar epithelial cells types 1 and 2 in the human lung is much higher than elsewhere in the body [23]. According to research, the level of ACE2 expressions in men is much higher than in women in alveolar cells [24]. Moreover, in their alveolar cells, ACE2 expression levels in Asians are much higher than in whites and African-Americans [25]. It is stated that Increasing ACE2 expression due to SARS-CoV-2 virus binding via spike protein could lead to alveolar cell damage and followed by systemic reactions and even death [26].

Nevertheless, the prerequisite for coronavirus attack on host cells is receptor binding. After binding to the receptor, the viral spike protein is cleaved by acid-dependent proteolysis by Cathepsin, TMPRSS2, or Furin Protease, followed by fusion of the viral coating with cell membranes. In general, the spike protein is structurally divided into two parts of the nS1 terminal unit containing a binding site to ACE 2 receptor in human cells (RBD) and the nS2 terminal region containing fusion protein and transmembrane anchor (T.A.) and intercellular tail (I.T.). Spike protein has a variable amino acid sequence that makes it more compatible with its host [27].

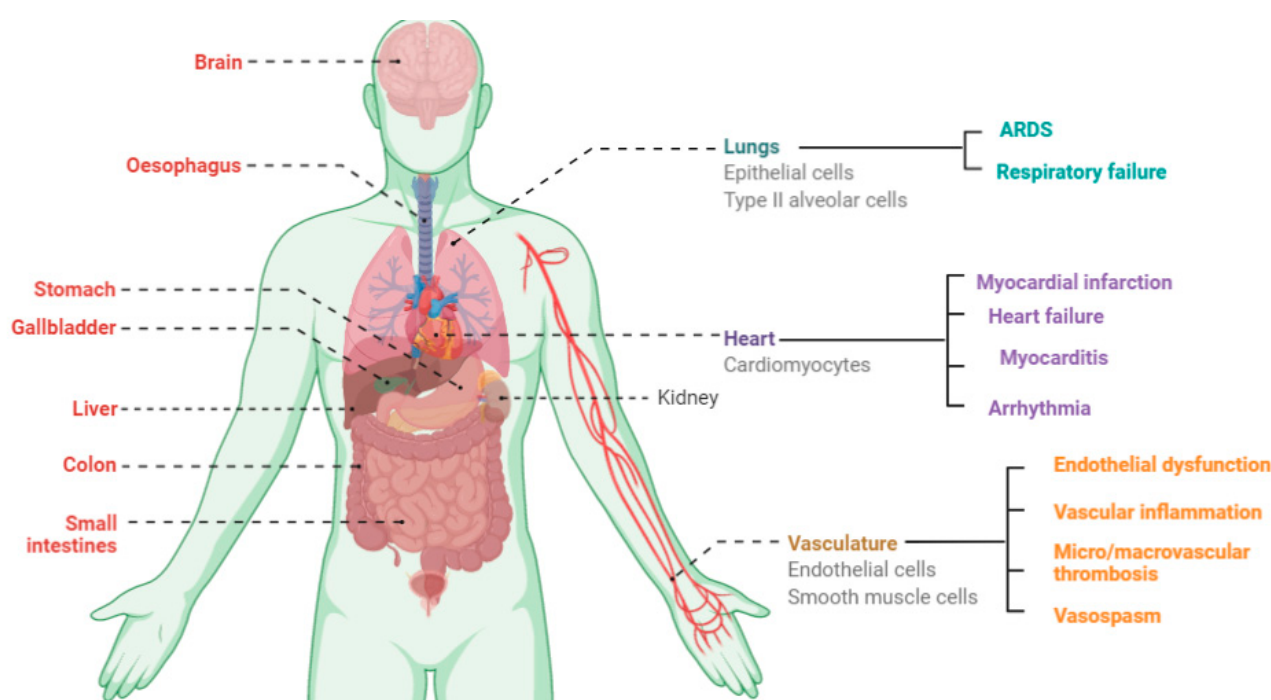


Figure 4. Multiple human host tissues that express ACE2 receptor highlighting lungs, heart, and vasculature. Note clinical consequences of viral infection in cardiovascular and respiratory tissue. ARDS, acute respiratory distress syndrome (Reprinted from “Expression of ACE2 Receptor in Human Host Tissues”, by [BioRender.com](https://www.biorender.com), accessed on 10 August 2020) [28].

3. Symptoms

Symptoms of COVID-19 disease vary from patient to patient. Sometimes it may be asymptomatic. Typically, in the early stages of COVID-19 infection, the most common infection symptoms can be fever, dry cough, and tiredness [29]. Less common symptoms are nausea or vomiting, muscle or joint pain, sore throat, loss of sense of smell or taste or both, nasal congestion, conjunctivitis, headache, different types of skin rashes, diarrhea, shivering, and dizziness [30]. In the disease’s progression stages, the patient will face severe shortness of breath, decreased blood oxygen (hypoxia), destruction of the lungs, and several organs dysfunction [31]. More severe and rare neurological complications such as stroke, encephalitis, delirium, and nerve damage are other complications of COVID-19 disease [32]. Figure 5 demonstrates the common symptoms of COVID-19.

Acute respiratory distress syndrome (ARDS) is the leading cause of COVID-19 induced mortality [33]. One of the most influential factors in developing ARDS with COVID-19 is a cytokine storm [34]. “Cytokine storm” is an aggressive inflammatory response associated with the secretion of large amounts of cytokines caused by the host’s immune response to the SARS-CoV-2 virus and is directly associated with lung damage, multiple organ failure, and severe COVID-19 prognosis [35].

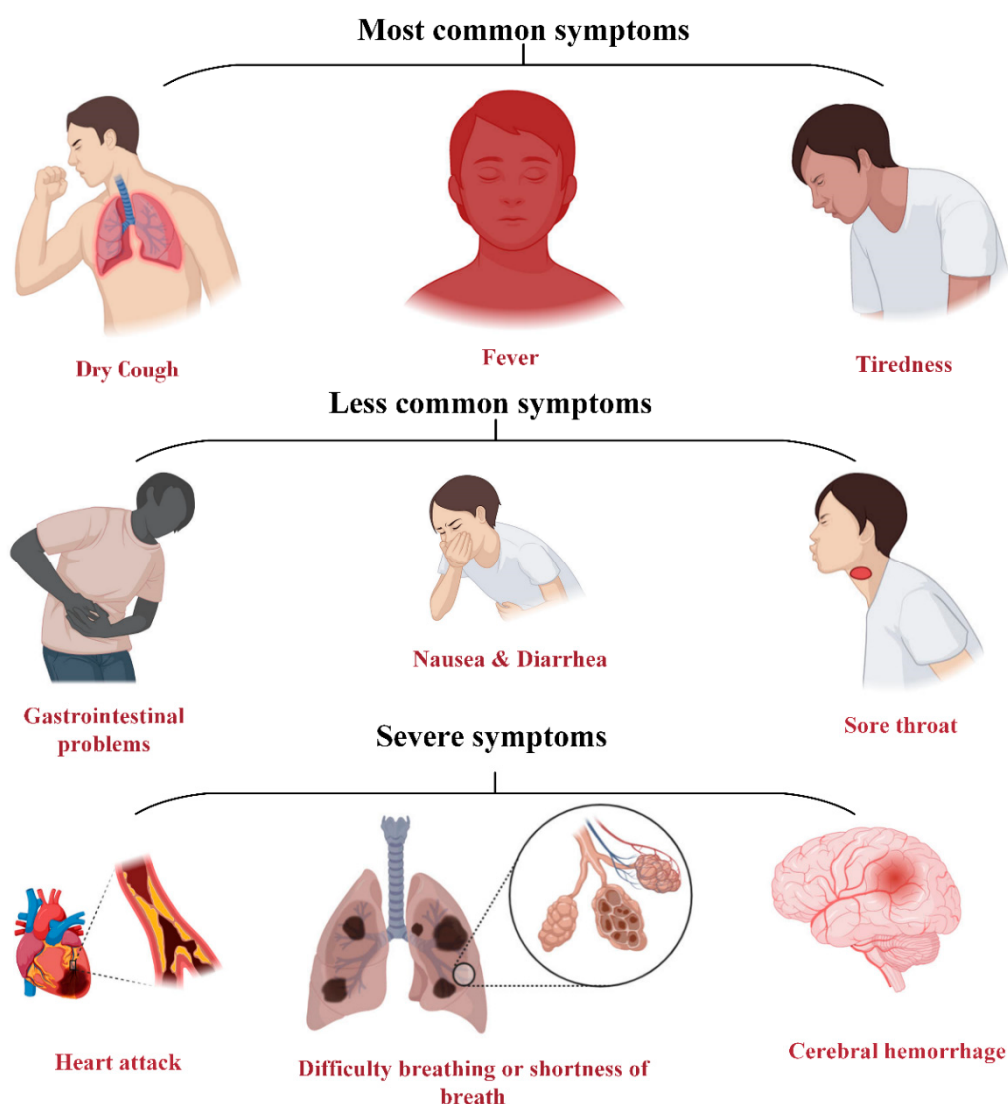


Figure 5. The most minor and major symptoms of COVID-19 (Created with [BioRender.com](https://www.biorender.com/), accessed on 15 March 2021).

After the virus enters the body through the mouth or nose, SARS-CoV-2 makes its way into the lungs and uses its distinctive spike proteins to infect alveolar cells. In response, the immune system attacks the infected area, killing healthy alveolar cells in the process. Reduced surfactant from alveolar epithelial type II cells, along with fluid accumulation due to the destruction of cells in the alveoli, causes reduced or severely hindered gas exchange. However, when cytokines are triggered without breaks, they can cause damage to the cells' responses to the cytokines and shut down the organs' function. This is known as a cytokine storm, which mediates severe disease, including COVID19 [36]. The following steps describe how a cytokine storm occurs in the lungs (Figure 6):

- (1) Infection of lung cells by COVID-19.
- (2) Cytokine production through virus detection by immune cells (macrophages).
- (3) Creating a cycle of inflammation in lung cells by further uptake of immune cells (white blood cells) through the cytokine phenomenon.
- (4) Fibrin formation and further damage.
- (5) Filling of the lung cavities due to the infiltration of fluids into the weak blood vessels, followed by respiratory damage.

Patients with mild symptoms improved after one week, while severe cases reported experiencing progressive respiratory failure due to alveolar damage caused by the virus, which may lead to death [37]. Mortality rates have been assigned averagely between middle-aged and elderly patients with the disease. According to WHO, recovery time for mild infections is about two weeks, and for severe infections three to six weeks [19].

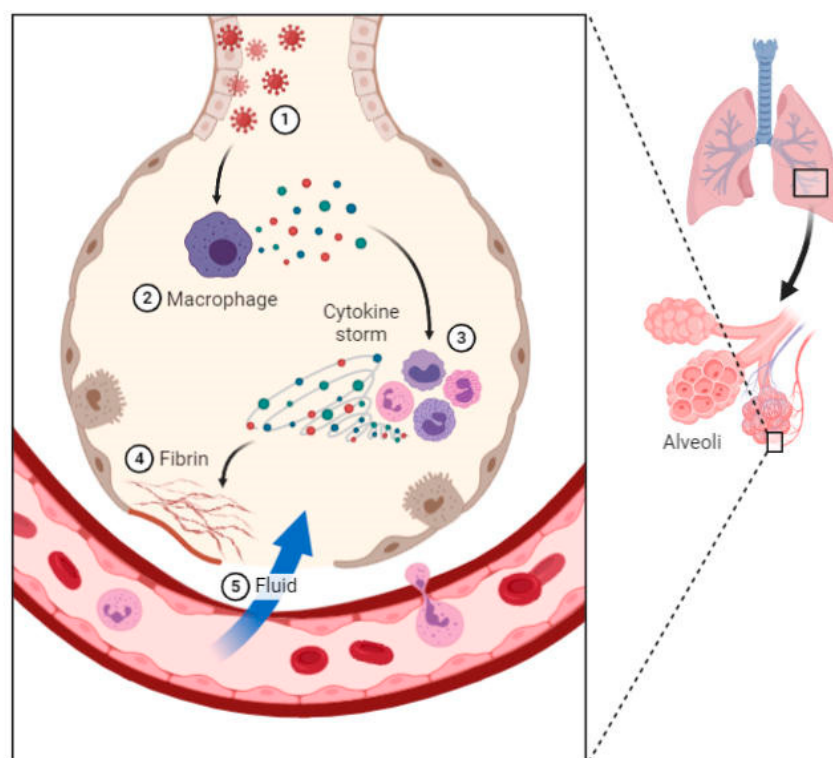


Figure 6. A cytokine storm in the lungs due to COVID-19 disease: (1) infection, (2) Cytokine production, (3) Creating a cycle of inflammation in lung cells, (4) Fibrin formation and (5) Filling of the lung cavities (Reprinted from “Cytokine Storm”, by BioRender.com, accessed on 3 July 2020) [38].

4. Transmission Routes

Due to the lack of specific treatment and preventing the disease’s outbreak, knowing the transmission methods can reduce the disease’s prevalence [39]. Epidemiologically, the SARS-CoV-2 outbreak could be related to the wholesale market of Hua Nan seafood and wet animals in Wuhan. Communities, health care and the family are the primary setting of human-to-human transmission of SARS-CoV-2 [40]. SARS-CoV-2 can be detected in various organs such as the eye, nasopharynx, saliva, alveolar lavage fluid, blood, intestine, and feces after infection [41]. Due to the high rate of transmission of SARS-CoV-2 and the uncertainty of the main routes of transmission, infection control and prevalence are facing significant challenges. According to research, close contact and respiratory droplets are one of the main ways of transmission. Therefore, the relevant experts strongly advised maintaining social distance and used a mask. Touching the face’s T-zone after contact with contaminated surfaces is also a mode of transmission that emphasizes the need for hand hygiene and handwashing. Other routes of transmission are through contaminated surfaces as well as airborne, fecal-oral transmission [42]. In general, droplet and contact route, airborne transmission, and fecal and oral have been identified to transmit the SARS-CoV-2 virus [43] (Figure 7).

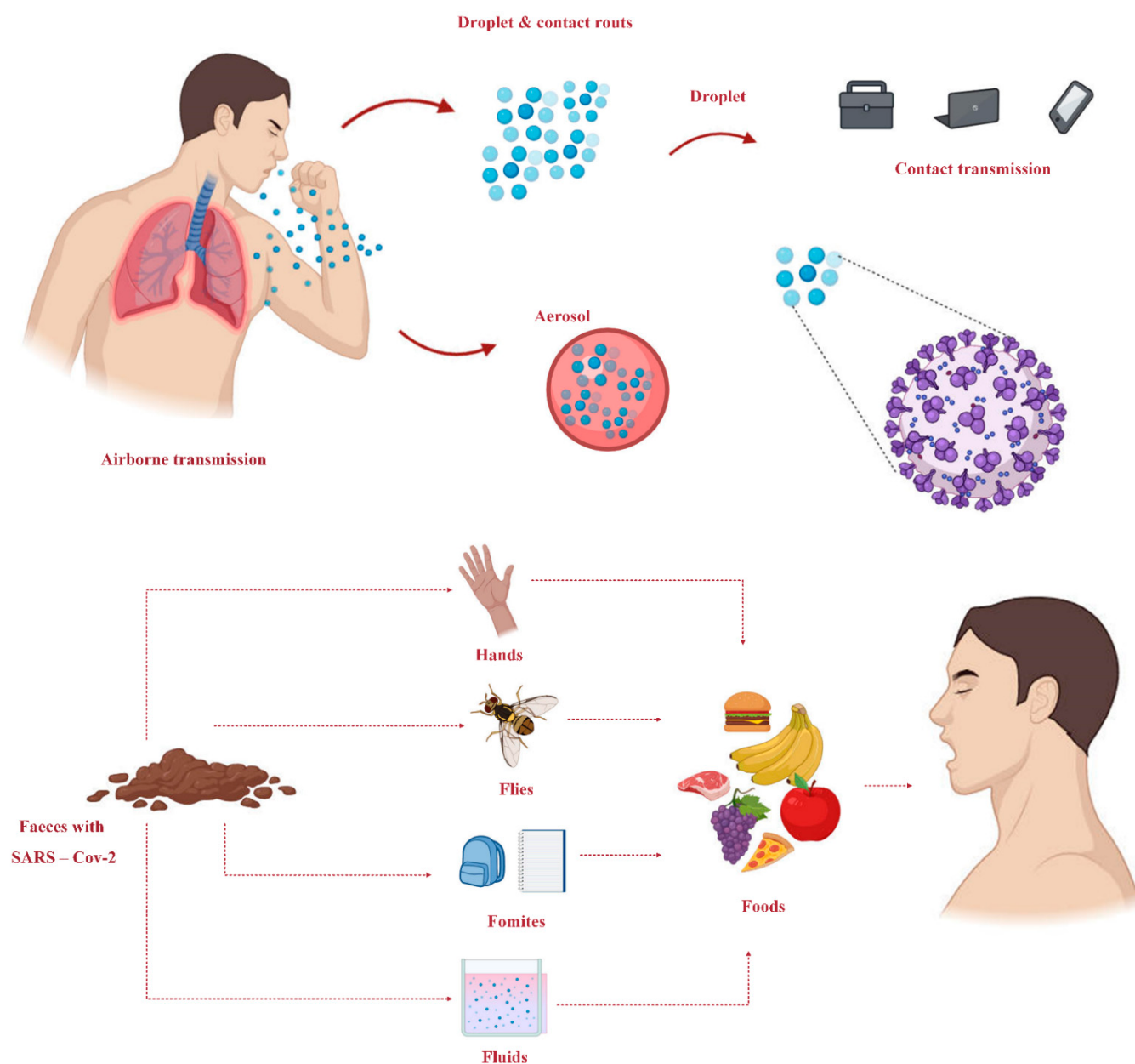


Figure 7. Schematic representation of SARS-CoV-2 Transmission Routes (Created with [BioRender.com](https://www.biorender.com/), accessed on 5 February 2021).

Droplet and contact routs: As mentioned, the main routes of transmission of the COVID-19 virus are respiratory droplets and close contact [44]. In general, the transmission of the COVID-19 virus through droplets and contact can be done in two ways: (1) direct contact with infected people and (2) indirect contact with surfaces used by an infected person. If the infected person does not observe the social distance (1 m) can make a healthy person sick through coughing or sneezing, the virus entering the mucous membranes of the mouth or nose, or Conjunctiva (eyes). Fomite can also be transmitted through household items such as clothing, utensils, and furniture around the infected person [45,46]. According to the Centers for Disease Control and Prevention (CDC) instructions in this section, it is necessary to observe the following points [47]:

- (1) Make sure the patient is in a convenient place.
- (2) The necessity of proper use of personal protective equipment (PPE).
- (3) Restrict the transportation and movement of patients as much as possible.
- (4) Utilization of disposable or patient care equipment as much as possible.
- (5) Prioritization disinfection and scouring of rooms.

Airborne transmission: Transmission of the virus through airborne particles is one of the main transmission routes of COVID-19 disease [48]. According to published research, if the suspended particles remain in the air for a long time, they will spread the virus [49]. In addition, World Health Organization stated that the virus could also be spread through aerosols in poorly ventilated indoors [50]. In closed environments (ICU rooms), airborne droplets or suspended particles in the air may infect the lungs when large doses of aerosols are inhaled [51]. The CDC's essential recommendations in this section are as follows [52]:

- (1) The necessity of keeping the patient in the air infection isolated room (AIIR).
- (2) limitation on the movement of health care personnel to patients' rooms.
- (3) The need for proper use of personal protective equipment (PPE).
- (4) Confine movement and transport of patients.
- (5) Immunization of people suspected of COVID-19 from unguarded contact.

Fecal and oral: As mentioned, gastrointestinal symptoms are a common symptom of COVID-19 disease [53]. Some patients with SARS-CoV-2 have the RNA virus in their stools [54]. Recent research has shown that SARS-CoV-2 in fecal samples from patients with COVID-19 can be another way of transmitting the virus. This transmission can occur through contact with food and contaminated water with fecal secretions [55]. Zhang et al. reported that the molecular diagnostic value of COVID-19 in a stool sample was equivalent to that of an oropharyngeal swab [56].

5. Prevention

Preventive measures due to lack of definitive treatment are of particular importance to prevent the spread of COVID-19 [57]. Several preventative measures have been taken at the public health level that can prevent or delay the transmission of COVID-19. These include quarantine of the infected person, identification and monitoring of contacts, disinfection of the environment, and utilization of personal protective equipment [58]. Table 1 reports the CDC recommendations for avoiding the outbreak of COVID-19 [59]:

Table 1. The CDC recommendations for preventing the spread of COVID-19.

Everyone Should	Description
Wash your hands	• Washing hands for at least 20 s with soap and water • Prior to preparing or consuming the food • In advance of touching your face • Posterior to utilization the toilet • When you leave a public place • After coughing, blowing your nose, and sneezing • Posterior to touching your mask • After changing a diaper • When caring for a sick person • Posterior to handling pets and animals • Use hand sanitizer (at least 60% alcohol) if the soap is not available
Stay away from close contact	• Indoors: prevent close contact with sick people and maintain a distance of 6 feet between the patient and other members of the home. • Outdoors: Maintain a 6-foot distance between yourself and people. • Warning: Asymptomatic disease vectors spread the virus.

Table 1. Cont.

Everyone Should	Description
The necessity of using masks to cover the mouth and nose in the face of others	• Prevent the high prevalence and infection of the virus by masks. • Due to the transmission of COVID-19 disease to others even if there are no symptoms. • The necessity of wearing masks in public areas and around people in society due to the difficulty of observing social distancing. • Do NOT use masks for employees of health centers and hospitals due to the importance of surgical masks and N95 respirators to prevent disease in staff. • Everyone should maintain social distancing in society because masks are not a suitable alternative to social distancing.
Cover coughs and sneezes	• Everyone should cover their mouth and nose with a handkerchief or hand when coughing or sneezing, and refrain from spitting in public places. • Never leave used napkins in public places and be sure to put them in the trash bin • Wash your hands regularly for at least 20 s and in the absence of soap and water, be sure to disinfect your hands with disinfectant solutions containing at least 60% alcohol.
Clean and disinfect	• Do NOT touch contaminated surfaces AND regularly clean, and disinfect surfaces that are frequently touched, such as telephones, keyboards, light switches, handles, faucets, sinks, toilets, tables, door buttons, and countertops. • Clean dirty surfaces with detergent or soap and water before disinfecting. • Use a household disinfectant as much as possible.
Monitor Your Health Daily	• Check your symptoms regularly, such as fever, cough, shortness of breath, or other symptoms of COVID-19, especially when travelling to high-risk areas. • If your symptoms develop, check your body temperature regularly. Be careful not to check your body temperature within 30 min of exercising or after taking fever medications such as acetaminophen. • If your symptoms develop, try to follow THE CDC guideline.
Protect Your Health This Flu Season	• The importance of influenza vaccination in winter and autumn months in 2020–2021 for the following reasons: • Reduction of the risk of influenza, hospitalization, and mortality. • Saving health resources to care for patients with COVID-19.

Studies have also fulfilled on the prevention of nosocomial infections and the psychological health issues associated with COVID-19. Nosocomial infections can be controlled by increasing awareness or prevention via personal protective equipment such as face and eye protection masks by medical staff at hospitals, disinfection of the tools, and placing classified protocols based on the infectious environment. Regarding mental health, some suggested psychological intervention in suspected and confirmed cases and medical staff [60] Figure 8 demonstrates different safety information about the COVID-19 infectious disease caused by the SARS-CoV-2 virus.



Figure 8. Infographic of various safety information about the COVID-19 infectious disease caused by the SARS-CoV-2 virus (Adopted from "COVID-19 Safety Information", by [BioRender.com](https://www.biorender.com/), accessed on 18 March 2020) [61].

6. Epidemiology

Epidemiologists' duties are essential when discovering a new infectious disease in collaboration with other scientists to determine the reasons for the spread of disease. Epidemiologists were initially present at the virus observation site for the first time (Wuhan, China) [62]. Then, they investigated the origin of the outbreak, control, and follow-up of the disease (such as new cases, hospitalizations, deaths, demographic information (such as symptoms, age, and gender, race/ethnicity, and treatment methods). In addition, they conducted clinical studies (including information from antibody testing, risk factors for severe illness, effective medical treatments) [62]. Finally, it takes necessary measures to slow the disease's spread (Supporting and assisting people in high-risk groups such as health care workers or the elderly to stay safe in environments such as grocery stores, home, or school) [62]. An overview of the various epidemiological statistics associated with seasonal influenza, SARS, MERS, and COVID-19 outbreaks are reported in Table 2. According to clinical research, and all ages are sensitive to COVID-19. It should be noted

that both symptomatic and asymptomatic patients could transmit the disease [63]. Studies have shown that the viral load is not significantly different between symptomatic and asymptomatic individuals [64].

Drops infected with the SARS-CoV-2 virus can be spread up to one to two meters and can be placed on surfaces in favorable weather conditions for many days. Nevertheless, in the face of common disinfectants such as sodium hypochlorite, hydrogen peroxide, etc., it is quickly eliminated [65]. According to a study on other COVID-19 traits, the disease's sensitivity on people depends upon age, physical health, and biological characteristics. Statistically, most adult patients are between 35 and 55 years old and are less common in infants and children. Among them, people with weaker immune function, the elders with an average age of 60 years and older, people with kidney and liver dysfunction [60] and hypertension, diabetes, asthma, chronic pulmonary obstruction, heart patients, smokers [63], pregnant women, and people with disabilities are at higher risk and more likely to be exposed to the virus [66]. Currently, there is a high potential for epidemics among humans; in other words, people of any age become infected with the coronavirus infection. In older people, the average mortality rate was higher with the diseases than in the young people [11]. There have been no reports of pregnant women receiving prenatal transplants or intrauterine [63]. According to the WHO, the consequences of not breastfeeding and separation between mother and child are more significant than the risk of COVID-19 infection in infants because the infection in infants is usually mild or asymptomatic. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breast feed. Mothers should be counselled that breastfeeding benefits substantially outweigh the potential risks for transmission [67–69]. Important epidemiological indicators associated with COVID-19 are reported in Table 3.

Table 2. Epidemiological comparison of respiratory viral infection [70–73].

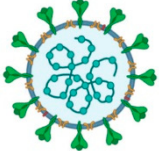
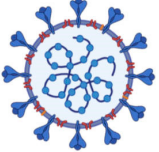
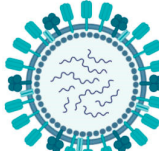
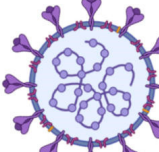
Disease	Disease-Causing Pathogen	R ₀ Basic Reproductive Number	CFR Case Fatality Rate	Incubation Time	Hospitalization Rate	Community Attack Rate	Annual Infected Global
SARS	 SARS-CoV	3	9.6–11%	2–7 days	Most cases	10–60%	8098 (in 2003)
MERS	 MERS-CoV	0.3–0.8	34.4%	6 days	Most cases	4–13%	420
Flu	 Influenza virus	1.3	0.05–0.1%	1–4 days	2%	10–20%	~1 billion
COVID-19	 SARS-CoV-2	2.0–2.5	~3.4%	4–14 days	~19%	30–40%	N/A ongoing

Table 3. Leading epidemiological indicators of COVID-19 research articles in January 2020.

Indicators	Description
❖ Age of patients	- Elderly (over 60 years old) [60]. - Mean age of 59 years (research conducted between patients 50 to 89 years) [74]. - Risk of a severe illness with increasing age of about 40 years [75]. - The low number of patients with mean age 0–49 years [76]. - Average age of patients was 55.5 years; age distribution: ≤39: 10%; 40–49: 22%, 50–59: 30%; 60–69: 22%, ≥70: 15% [77]. - In terms of age distribution, 1% under 10, 1% 10–19, 8% 20–29, 87% 30–79, and 3% >80 [78]. 50–60 (More than half a million COVID-19 patients from different countries participated in this meta-analysis) [79]. - Cases range from 2 to 72 years [80]. - Increased incidence with increasing age over 60 years [81]. - The median age of was 74 years [82]. - Cases range aged between 35 and 55 years [83].
❖ Sex of patients	More cases were males [84,85].
❖ Mortality rate	- Increased mortality between 60 and 80 years [86–88] - The mortality rate was significantly high in the age range of >60 years [75,89].
❖ Incubation time	- Average of 7 days (2–14 days) [60,90]. - Average of 10 days [91]. 6.4 days (95% CI 5.6–7.7 days), with a range of 2.1–11.1 days [92]. 5.0 days (95% CI 4.4–5.6 days), with a range of 2–14 days [92]. 4.0 days, with a range of 1–7 days [93].

7. Diagnosis

Because of the lack of definitive curative treatment for this disease, the most effective solution after preventing and controlling is the timely diagnosis of the disease and isolating the illnesses. There are several ways to diagnose the disease early, such as the RT-PCR method, CT-Scan, Serological antibody blood test, and Artificial intelligence.

7.1. RT-PCR Method

One of the most important ways to detect the SARS-CoV-2 virus in upper and lower respiratory specimens is the Real-Time Reverse Transcriptase (RT)–PCR Diagnostic Panel. The basis of the PCR is copying the RNA and DNA structure of the sample, which can diagnose infectious origin and various genetic and blood diseases [94]. Figure 9 demonstrates COVID-19 diagnostic testing through real-time RT-PCR. As depicted in Figure 9, there are five necessary steps to perform the test: sample collection, RNA extraction, RT-qPCR set up, and test results, all of which can be customized to explain both this and other RT-qPCR diagnostic protocols. The steps for performing the RT-qPCR test are as follows [95]:

Nasopharyngeal swab <15 min: Cotton swab is inserted into the nostril to absorb sections.

Collected specimen 0–72 h specimen is stored at 2–8 °C for up to 72 h or proceed to RNA extraction.

RNA extraction ~45 min purified RNA is extracted from the deactivated virus.

RT-qPCR, ~1 h per primer, set purified RNA is reverse transcribed to cDNA and amplified by qPCR.

Test results real-time positive SARS-CoV-2 patients cross the threshold line within 40.00 cycles (<40.00 Ct).

This method aims to detect the nucleic acid present in the nasal swab sampling or the respiratory tract using the PCR process in real-time. It is confirmed based on the reproduction function and sequence of the virus in the sample [96].

Because the infectious virus infects the host's respiratory system, the necessary samples are taken from the lower and upper respiratory tract. The swab test is sampling with a special swab from the throat and nose of a person. The sampling of the nasal aspirates and lungs is implementing by injection of a saline solution into the nose, and then the

sample is collecting by suction. Finally, if it is necessary to continue the sampling, the lower respiratory tract, i.e., Bronchoalveolar lavage or chip aspiration, which is sputum sampling, is performing [19,63]. The RT-PCR is widely used in the diagnostic field, and the error percentage of the method is meagre [97].

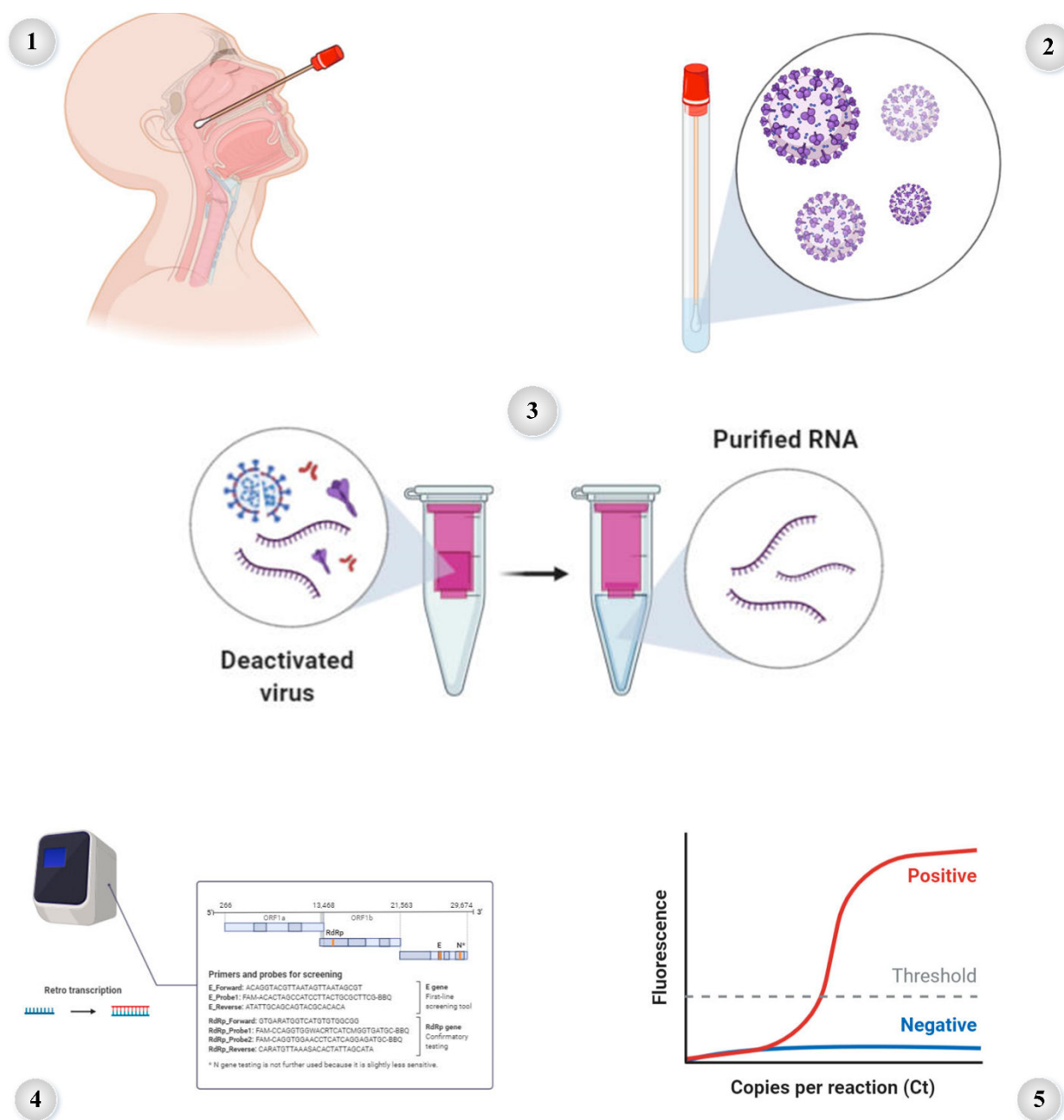


Figure 9. The protocol template COVID-19 diagnostic testing through real-time RT-PCR: (1) Nasopharyngeal swab, (2) Collected specimen, (3) RNA extraction, (4) purified RNA and (5) Test results real-time (Adopted from “COVID-19 Diagnostic Test through RT-PCR”, by BioRender.com, accessed on 9 April 2020) [98].

7.2. CT-Scan

Computed tomography (CT) is a suitable diagnostic method that sheds light on several stages of disease diagnosis and development [99]. One way to look at the morphological patterns of lung lesions associated with COVID-19 is through chest scans such as X-rays and computed tomography (CT) scans. It should be noted that the accuracy of diagnosis depends heavily on specialists [100]. In the early stages of the epidemic in any country,

the use of CT imaging methods was more critical than RT-PCR due to the lack of RT-PCR technology or the lack of kits and diagnostic equipment suitable for accurate sampling [101]. In addition, CT images are a valuable tool to help physicians identify internal structures and examine their shape, size, density, and texture [102].

Moreover, CT imaging can help to reveal the abnormalities caused by COVID-19. In about 85% of patients with superimposed irregular lines and interfaces, Chest CT in COVID-19 pneumonia cases shows bilateral, peripheral, and basal predominant ground-glass opacities (GGOs) and/or consolidation [103]. In addition, in patients without severe respiratory distress who recovered from coronavirus disease 2019, chest CT scans revealed that the greatest severity in lung abnormalities occurred after about ten days from the initial symptoms [104]. It is essential to pay close attention to asymptomatic patients as they can transmit the infection quite easily if they are undetected. CT imaging of these patients has unique features that can be detected even in asymptomatic patients with negative nucleic testing [105]. Figure 10 shows the positive and negative COVID-19 CT scan results of the patient.

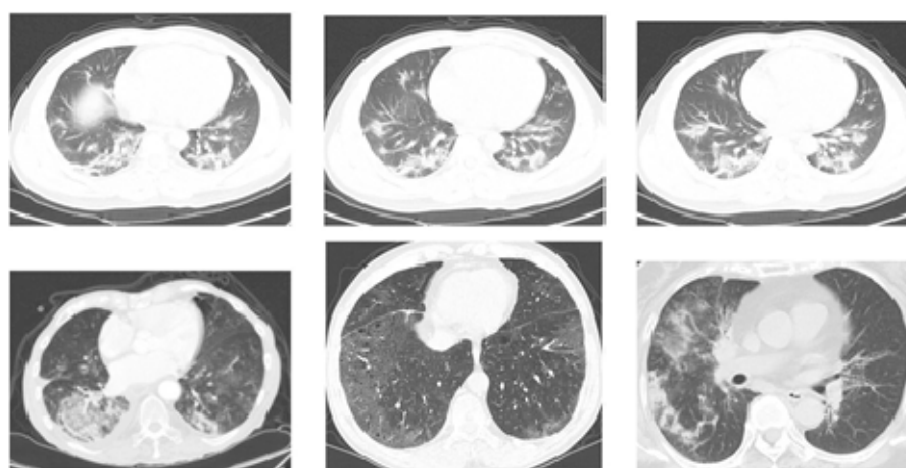


Figure 10. Examples of CT images that are positive for COVID-19 (top) and non-COVID-19 (bottom) from the COVID-CT dataset, reprinted from [106], Copyright 2020, Elsevier.

7.3. The Serological Antibody Blood Test

Serology testing is a diagnostic method for detecting antibody-mediated immune responses against infectious agents [107]. The European Center for Disease Control and Prevention (ECDC) has approved the COVID-19 serological test for epidemiological and monitoring purposes only because it does not detect the early stages of infection [108]. Rapid serological testing can be considered an alternative to molecular testing to identify COVID-19 patients when access to PCR testing is limited or non-existent. The use of serological tests with low prevalence is not appropriate because this method is likely to have false-positive results compared to the actual positive [109]. This protocol template (Figure 11) demonstrates COVID-19 serologic diagnostic testing through antibody detection. It depicts sample loading, SARS-CoV-2 antibody-antigen detection, and qualitative test results. This can be customized as a whole to explain other serologic diagnostic protocols for different viral, bacterial, or parasitic pathogens [110]. The steps for performing a serology test shown in Figure 11 are as follows [111]:

- (1) **Sample loading:** add a drop of blood or serum in the sample well (S).
- (2) **Buffer loading:** add dilution phosphate saline buffer to sample well.
- (3) **Sample incubation:** capillary action moves sample across lateral flow test.
- (4) **Antibody-antigen recognition:** antibodies with specificity for COVID-19 bind to gold COVID-19-antigen conjugates in the conjugate pad.
- (5) **COVID-19 antibody detection:** sample enters testing well (T), and COVID-19 antibody-antigen complex binds to immobilized anti-human IgG/IgM antibodies.

- (6) **Control antibody detection:** rabbit antibody-gold conjugate binds to immobilized anti-rabbit IgG antibodies.
- (7) **Interpreting results:** **Positive:** one strip each in C well and T well, **Negative** = one strip in C well.

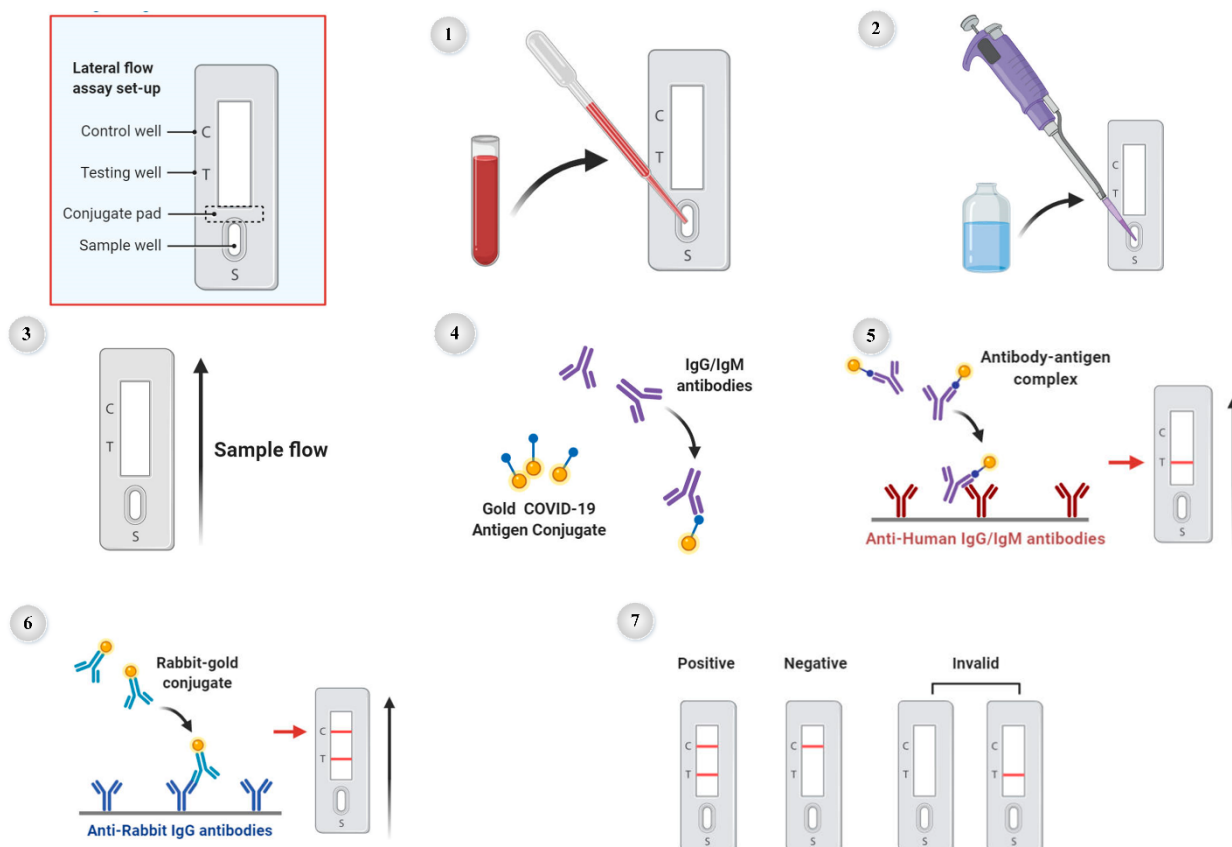


Figure 11. Schematic of serological testing steps: (1) Sample loading, (2) Buffer loading, (3) Sample incubation, (4) Antibody-antigen recognition, (5) COVID-19 antibody detection, (6) Control antibody detection and (7) Interpreting results: Positive (Reprinted from “COVID-19 Serologic Diagnostic Test through Antibody Detection”, by [BioRender.com](#), accessed on 2 January 2020) [112].

7.4. Artificial Intelligence (AI)

In the COVID-19 pandemic, the development of new technologies to monitor and control the outbreak of COVID-19 (coronavirus) is a significant step taken by medical researchers. Artificial intelligence (AI) in medicine has recently led to significant advances in diagnosis, biotechnology, and drug production [113]. AI technology has shown promising prospects for various epidemics (SARS, EBOLA, and HIV) [114]. The COVID-19 crisis and the rapid increase in the number of new and suspected cases have led to the rise in AI technology used to control and diagnose the disease [99,115]. Artificial intelligence can quickly detect the symptoms of the disease and alert patients and health authorities. In this way, it can reduce the decision time in traditional disease diagnosis processes [116]. In these studies, artificial intelligence mainly uses medical imaging technologies such as computed tomography (CT), X-ray imaging (X-ray), and magnetic resonance imaging (MRI) to diagnose infected cases [117]. Moreover, AI can take practical steps in tracking the coronavirus's spread, identifying high-risk patients, adequately analyzing patients' previous data, and predicting the risk of death [118]. Table 4 demonstrates the main applications of AI in Pandemic COVID-19.

Table 4. Main applications of AI in COVID-19 pandemic.

Properties	Description
❖ Primary diagnosis and detection of the infection [119,120]	• Rapid analysis of patients' irregular symptoms • Facilitating to identify suspected infection cases through medical imaging such as computed tomography (CT), magnetic resonance imaging (MRI).
❖ Monitoring the treatment [121,122]	• Assist in automated outbreak monitoring and prediction • Establish a neural network to extract visual features and assist in appropriate monitoring and treatment of patients • Follow-up patient updates and follow-up solutions for the COVID-19 pandemic.
❖ Contact tracing of the individuals [117,123]	• Analyze infected surfaces and hotspots • Provide to predict disease progression
❖ Projection of cases and mortality [124,125]	• Predict the nature of the virus through existing data, social media, and media platforms • Tracking the risks of infection and the possibility of spread • Predict the number of positive cases and deaths in different areas • Identify vulnerable areas and help the people of that area
❖ Development of drugs and vaccines [126–129]	• Analysis of existing data on COVID-19 for pharmaceutical research • Provide real-time acceleration of drug testing • Help identify drugs useful for treating COVID-19 patients • Design diagnostic tests and assist in the production of vaccines
❖ Reducing the workload of healthcare workers [130–133]	• Reducing the workload of healthcare workers • Training students and physicians in early diagnosis and providing early-stage treatment using digital methods
❖ Prevention of the disease [117]	• Update information • Predict possible sites of infection • Help prevent viruses and diseases in the future, with the help of previous data

8. The Role of Nanotechnology in Diagnostics and Treatment of COVID-19

Nanotechnology is currently used to diagnose, treat, control, and prevent medical science diseases [134]. Figure 12 represents the applications of nanotechnology in the face of COVID-19 disease. Properties of nanoparticles such as high solubility, small size, surface adaptability, and versatility are used to produce safe and high-quality drugs, targeted tissue therapies, personalized nanomedicines, and early diagnosis and debarment diseases [135]. Nanotechnology can play a unique role in identifying, treating, and preventing COVID-19. Essential properties of nanoparticles that can be mentioned in the fight against COVID-19 are [135]:

- (1) Design of safe personal protective equipment (PPE) to prevent infection and increase healthcare workers' safety.
- (2) Production of antiviral disinfectants and surface coatings that inactivate the virus and prevent its spread.
- (3) Design of precise and sensitive nano-based sensors for rapid detection of infection or immunological response.
- (4) Production of new drugs to increase activity, reduce toxicity, and continuous release.
- (5) Targeting drug delivery.
- (6) Vaccination production (enhancement of humoral and cellular immune responses).

Table 5 reported the advantages and disadvantages of nanotechnology in the face of COVID-19.

Table 5. The advantages and disadvantages of nanotechnology in COVID-19.

Properties	Advantages	Disadvantages
❖ Nanomaterials for surface decontamination	- Progression of effective and promising disinfection process (Antimicrobial activity), Development of new materials, expansion of self-cleaning properties of surfaces (Release of chemical disinfectants to increase their duration of action) [136]. - Antiseptic, Antimycotic Agent, and antiviral activity of metal nanoparticles [137]	- Expandability and manufacture costs - Issues related to intellectual and regulatory characteristics - Toxicity and environmental impacts of these systems [138]
❖ Development of nanomaterials for personal protective equipment (PPE)	- Participate in the production of appropriate masks and gloves [139] - Use equipment more efficiently, more resilient, and safely against biological and chemical hazards [140] - Lack of effect on texture and breathability of materials due to antimicrobial activity and hydrophobicity [141]	- Skin irritation - Allergies - Toxic effects in humans - Environmental pollution (release of nanoparticles during washing from clothes) [135]
❖ nanotechnology for virus detection and disease diagnosis	- Improving the quality of SARS-CoV-2 diagnosis (Reduce the duration of diagnosis and increase the scope of diagnosis) [142] - A useful tool for the production and development of various diagnostic kits in COVID-19 [143] - develop of the sensors for the detection of SARS-CoV-2 [135,144]	high operating expenses and capital expenditures
❖ Carriers and drug delivery systems	- Transfer of the drug to the target organ - Enhance the antiviral effects of drugs - Very effective antiviral formulation - Reduction of side effects and toxicity of the drug - Control the cytokine storm [145] - Increase the half-life of the drug	
❖ Nanoparticles design for virus inhibition	- Improve action and reaction with viral particles - Interference with their entry into cells - Enhance bioactivity and consistency of compounds - Release of antiviral agents in a controlled manner - Inhibition of the virus in the reproductive stage	
❖ Development of vaccines	- Protects antigens versus precocious demolition - Continuous release - Increase antigen consistency - Targeted immunogenic delivery - Increased uptake by antigen-presenting cells (APCs) [146] - Use of various materials to produce Nanocarriers such as polysaccharides, polymers, and lipids [147] - Protect DNA or RNA versus enzymatic demolition and enhancement cell absorption [148] - Release of genetic material in target cells - Increasing the compatibility of vaccines by changing the properties of nanoparticles	

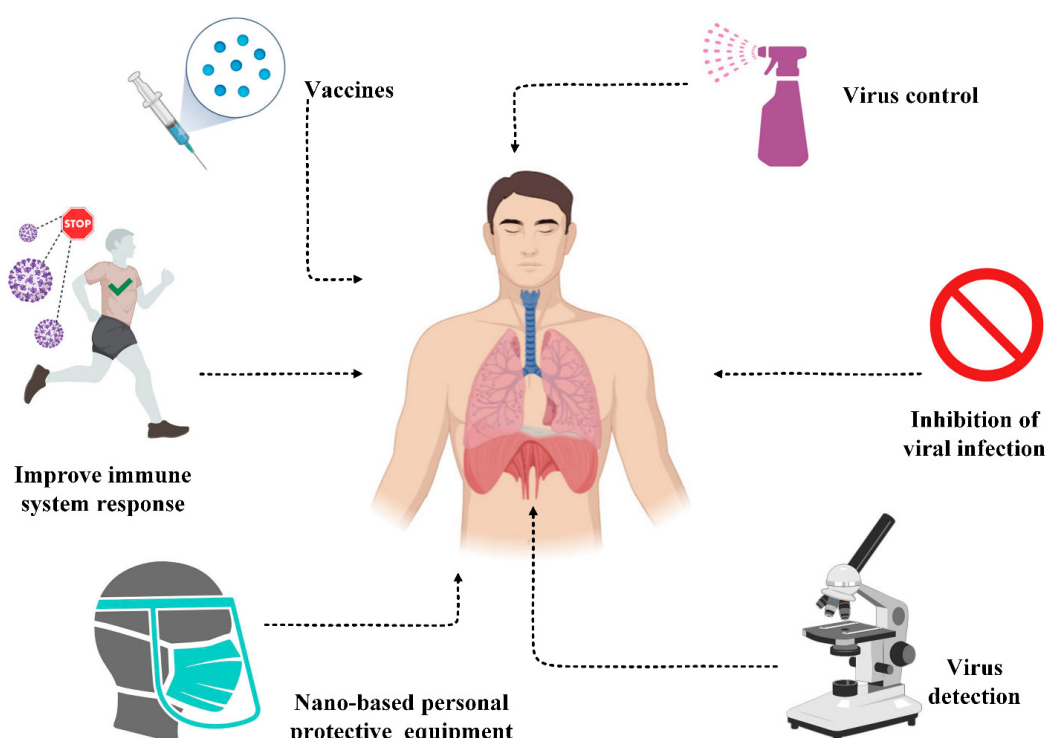


Figure 12. Schematic representation of the nanotechnologies tools to prevent and control COVID-19 (Created with [BioRender.com](https://www.biorender.com/), accessed on 13 February 2021).

It should be noted that nanoparticles (NP) have been widely used in many medical applications such as biosynthetic sensors, drug delivery, imaging, and antimicrobial therapy [149]. Table 6 reports the types of NPs and their applications in the detection, control, and vaccination against coronaviruses.

Table 6. The types of NPs and their applications in the detection, control, and vaccination against coronaviruses.

Properties	Type of NPs	Description
Nanoparticle for diagnostic	Metal NPs	- Development of a colorimetric assay based on gold nanoparticles (AuNPs) [150]. - Development of the nanoplasmonic pillar arrays (NPA) comprise gold Nano islands [151].
	Carbon nanotubes	- Fabrication of nanosensor based on non-mediated SWCNTs with ACE2. These ACE2-SWCNT nanosensors can be turned into an optical tool for prompt diagnosis of SARS-CoV-2 [152]. - Use in electrochemical sensors based on functional cobalt TiO₂ nanotubes (Co-TNTs) for prompt diagnosis of SARS-CoV-2 via sensing the spike (receptor-binding domain (RBD)) present at the virus surface [153].
	Silica NPs	- Antiviral effects against SARS-CoV-2 on face masks [154]. - Use of silica-coated superparamagnetic nanoparticles to detect the virus [155].
	Quantum dots (QDs)	- Use of QD nanoparticle probes to identify and confirm SARS-CoV-2 Spike and ACE2 receptor binding inhibitors in human cells [156]. - Designation of human IgG and to investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific IgM and IgG [157].
	Magnetic NPs	- Fabrication of the surface-functionalized magnetic nanoparticles (MNP's) and viral RNA-extraction protocol for potential detection of COVID-19 [158]. - Development of pcMNPs-based viral RNA elicitation method for the sensitive diagnosis of COVID-19 causing virus, the SARS-CoV-2 [159].
	Graphene	- The role of graphene-based materials and strategies in fluid biopsy and diagnosis of viral diseases in the diagnosis of COVID-19 [160]. - Use of graphene effect transistors (GFET) to detect SARS-CoV-2 in human nasopharyngeal swab samples. - Use of laser engraved graphene for rapid and remote evaluation of COVID-19 biomarkers [161].

9. Treatment

The treatments available for people with COVID-19 are based on their symptoms, and there is no exact treatment available for complete recovery in patients with COVID-19. Researchers and physicians are making efforts to provide proper treatment for COVID-19 patients [162]. Researchers are testing a wide range of possible therapies, including antiviral medicines, immunosuppressants, monoclonal antibodies, and vaccines [163]. In the early stages of the disease, the patient's immune system is challenged to prevent replication of the SARS-CoV-2 virus; however, in the acute stages, maybe experience tissue damage due to severe immune/inflammatory reactions [164]. According to clinical research, antiviral therapies are most effective in the early stages of the disease. In contrast, immunosuppressive/anti-inflammatory treatments are likely to be most effective in the severe stages of COVID-19 [165]. It should be noted that anti-SARS-CoV-2 antibody-based therapies are more effective in the early stages of infection before the patient enters the acute phase. Therefore, physicians have recommended receiving monoclonal antibodies against SARS-CoV-2 [166]. The drugs approved by the US Food and Drug Administration (FDA) are Dexamethasone and Remdesivir. It is recommended for hospitalized patients who need supplemental oxygen [167]. Remdesivir is an intravenous nucleotide drug from the adenosine analogue [168]. The mechanism of action of Remdesivir against the SARS-CoV-2 virus is presented in Figure 13. As depicted in Figure 13, Remdesivir binds to RNA-dependent RNA polymerase and prevents virus replication by premature termination of RNA transcription [168]. In the acute phase of the disease, when patients need a ventilator, dexamethasone, a corticosteroid, significantly affects patients' recovery [169]. All recommended treatments for COVID-19 are reported in Table 7.

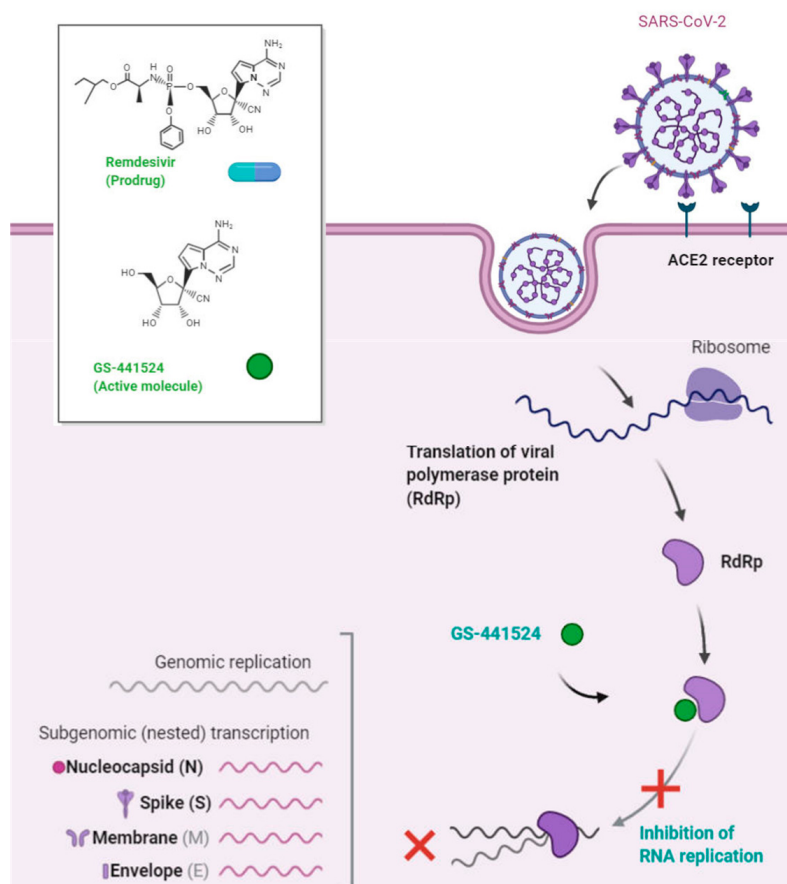


Figure 13. The potential mechanism of action of Remdesivir against coronavirus replication (Reprinted from “Remdesivir: Potential Repurposed Drug Candidate for COVID-19 (Portrait)”, by BioRender.com, accessed on 1 April 2020) [170].

Table 7. All recommended treatments for COVID-19.

Properties	Type	Description
Drug treatment	Remdesivir	- Due to its ability to inhibit SARS-CoV-2, one of the promising drugs for COVID-19 [171,172]. - Adults who are hospitalized and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). - Pediatric patients who are hospitalized (aged < 12 years and weighing 3.5 kg to < 40 kg) [173]. - Side effects (gastrointestinal symptoms (e.g., nausea), increased transaminase levels, increased prothrombin time and hypersensitivity reactions, control of renal function, drug interaction with chloroquine or hydroxychloroquine) [168,174]. - Low side effects in pregnant women [175].
	Favipiravir	- Favipiravir is a promising drug for COVID-19 that decreases hospital stay and the need for mechanical ventilation [176]. - Favipiravir may emerge as a valuable drug in the treatment of mild to moderate symptomatic SARSCoV-2 infected cases [177]. - The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1st day, followed by 800 mg orally twice daily, up to a maximum of 14 days. The 14-day course in India costs Rs 10,200 [177].
	Chloroquine or Hydroxychloroquine	- Chloroquine is an antimalarial drug (manufactured in 1934). Hydroxychloroquine, an analogue of chloroquine (manufactured in 1934). - Less toxicity of hydroxychloroquine compared to chloroquine [178]. - Prevents acute coronavirus 2 (SARS-CoV-2) syndrome by increasing endosomal pH [179]. - Chloroquine is a suitable inhibitor of Angiotensin-converting enzyme 2 (ACE2) [180]. - Inhibits the transfer of SARS-CoV-2 from primary endosomes to end lysosomes and prevents the spread of viral genomes [181]. - The COVID-19 Treatment Guidelines Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI) [182]. - Non-recommendation for use in nonhospitalized patients [178]. - high-dose chloroquine (600 mg twice daily for ten days). - Side effects: QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths [183], fluoroquinolone antibiotics [184], Prolongation of QTc interval with concomitant use of hydroxychloroquine and azithromycin [179,185], Increased risk of cardiac arrest if concomitant use of hydroxychloroquine with azithromycin [186]. - Drug-Drug Interactions: Caution in concomitant use with drugs metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) [187].
	Lopinavir/ritonavir	- Prevent severe acute respiratory syndrome-associated coronavirus (SARS-CoV-2) IN VITRO condition [173,188,189]. - No recommendation for use by the COVID-19 Treatment Guidelines for the treatment of COVID-19, except in a clinical trial [190]. - Side effects (Nausea, vomiting, diarrhea (common), QTc prolongation, Hepatotoxicity) [190]. - Drug and drug interactions (Increased drug concentration with concomitant use of drugs metabolized by cytochrome P450 3A enzyme and increased toxicity) [190].

Table 7. Cont.

Properties	Type	Description
Immune-Based Therapy [165]	Ivermectin	- Ivermectin, an FDA-approved anti-parasitic (broad-spectrum anti-viral activity in vitro, an inhibitor of the causative virus (SARS-CoV-2)) [174,191,192]. - No recommendation for use by the COVID-19 Treatment Guidelines for the treatment of COVID-19, except in a clinical trial [192].
	Blood-derived products	- Use of blood-derived products of people recovered from SARS-CoV-2 infection(convalescent plasma, immunoglobulin products) [179] (The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the use of convalescent plasma for hospitalized patients with COVID-19). - Neutralizing monoclonal antibodies (clinical trials) [193,194].
	Immunomodulatory therapies	- Use of drugs to treat immune and/or inflammatory syndromes such as corticosteroids (e.g., glucocorticoids) [195]. - Targeted anti-inflammatory treatments such as interleukin inhibitors [184], interferons [196], kinase inhibitors [197]. - Tocilizumab is a suggested anti-inflammatory drug to treatment COVID-19 [198].
	Baricitinib	Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating clinical status improvement among patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events [199].
Anti-SARS-CoV-2 Antibody Products	Bamlanivimab	- Bamlanivimab and etesevimab are neutralizing monoclonal antibodies that bind to different but overlapping epitopes in the receptor-binding domain of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The bamlanivimab plus etesevimab combination blocks SARS-CoV-2 entry into host cells and is being evaluated for the treatment of COVID-19 [200]. - On 9 February 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make bamlanivimab 700 mg plus etesevimab 1400 mg available for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the EUA criteria for use of the products below). The issuance of an EUA does not constitute FDA approval of a product [200].
Corticosteroids	Dexamethasone [201]	- In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. - There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
	- Methylprednisolone - Prednisone - Hydrocortisone	- If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be used [202]. - Methylprednisolone: [A total of 102 severe and critically ill COVID-19 patients were included in this study. The results showed that methylprednisolone treatment did not improve the prognosis] [203]. - Hydrocortisone is commonly used to manage septic shock in patients with COVID-19 (The hydrocortisone dose was adjusted according to clinical response).

Table 7. Cont.

Properties	Type	Description
Adjunctive Therapy	Antithrombotic Therapy [204]	- Chronic Anticoagulant and Antiplatelet Therapy. - Not used for non-hospitalized patients with COVID-19. - Undecomposed heparin, low molecular weight heparin, and warfarin are not contraindicated in children and pregnant women. - Prohibition of oral anticoagulants with direct action.
	Vitamin C [187]	The potential designation of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19.
	Vitamin D [205]	- Increased risk of pneumonia in patients with low levels of vitamin D [190,206]. - Use of vitamin D supplementation to protect against acute respiratory tract infection [207].
	Zinc [208]	- There are insufficient data to recommend either for or against the use of zinc to treat COVID-19 [208]. - The COVID-19 Treatment Guidelines Panel recommends against using zinc supplementation above the recommended dietary allowance to prevent COVID-19, except in a clinical trial (BIII) [208]. - Evaluation in clinical trials of zinc supplement alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19 [209].

10. Vaccines

A vaccine is a biological product that produces an acquired active immunity against a specific microbial disease [192]. Vaccines are very vital to save the lives of millions of people every year. The primary function of vaccines is to train and prepare the immune system to identify and fight the target viruses and bacteria. Common components of vaccines are as follows (Figure 14):

- (1) **Active ingredients** Viral or bacterial antigens that directly stimulate the immune system but cannot cause disease.
- (2) **Adjuvants** Aluminum salts in small quantities that help to boost the immune response to the vaccine.
- (3) **Antibiotics** prevent contamination by bacteria during the vaccine manufacturing process.
- (4) **Stabilizers** Sugar/gelatin keeps the valuable vaccine until it is administered to a patient.
- (5) **Preservatives** Thimerosal prevents dangerous bacterial or fungal contamination (only used for influenza vaccines).
- (6) **Trace components** Residual inactivating ingredients such as formaldehyde, and residual cell culture materials (present in small quantities that do not pose a safety concern).

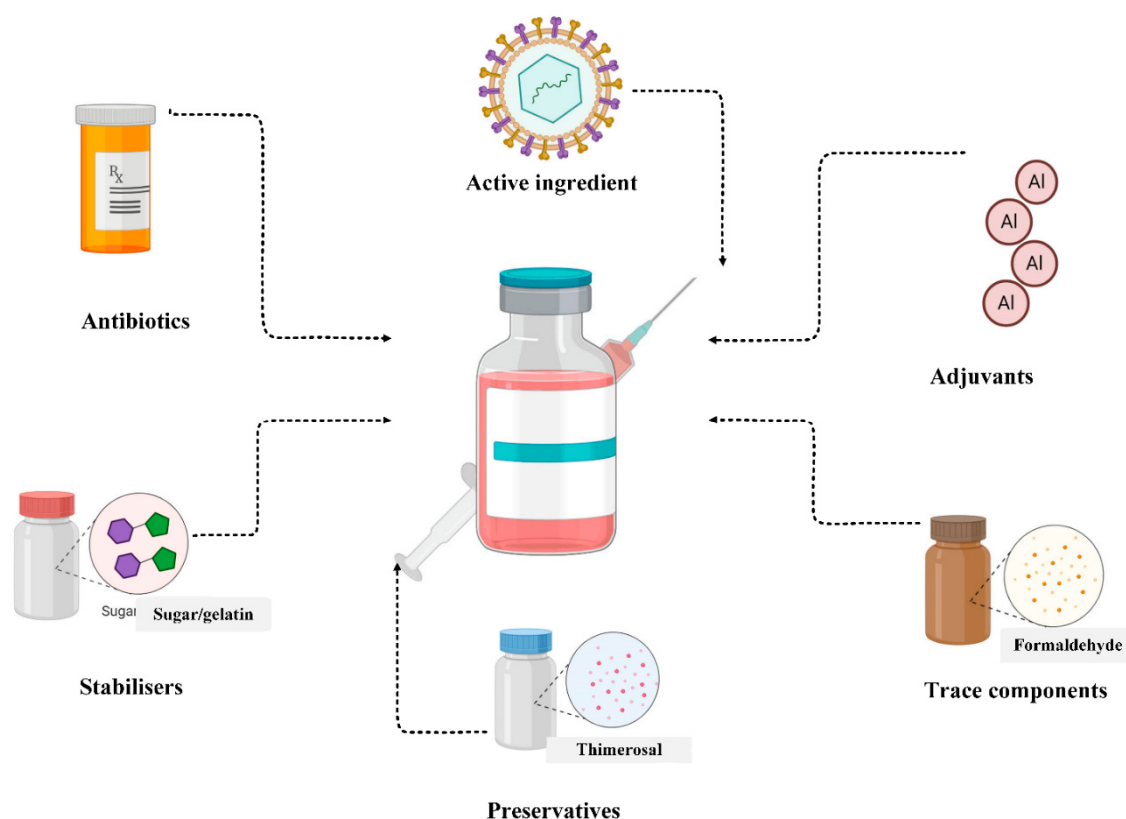


Figure 14. Common components of Vaccines (Adopted from “Common Components of Vaccines”, by [BioRender.com](#), accessed on 7 April 2020).

According to the WHO, there are currently more than 50 COVID-19 vaccine candidates in trials. To accelerate and distribute the vaccine equitably, WHO is working with scientists, businesses, and global health organizations through the COVAX (Working for global equitable access to COVID-19 vaccines) project (led by WHO, GAVI CEPI). BNT162b2 (Pfizer-BioNTech) developed by BioNTech and manufactured and distributed by Pfizer, and Fosun Pharmaceutical is the first EUA-approved COVID-19 vaccine for emergency use. Clinical trials were performed on 44,000 people, which is reported to be more than 95% successful [210,211]. It should be noted that the Moderna vaccine was authorized for emergency use on 18 December 2020, by the US Food and Drug Administration (EUA) to prevent COVID-19 disease. The AZD1222 vaccine developed by Oxford [212] is another effective vaccine that has just received an emergency license. The vaccine has been clinically tested on 65,000 people and is reported to be more than 70% effective against COVID-19 Acute Respiratory Syndrome [213]. Authorized/approved COVID-19 vaccines are tabulated in Table 8. The mechanism and type of process of the approved BNT162b2, Sinopharm and Oxford/AstraZeneca vaccines are presented in Figure 15.

Table 8. Authorized/approved COVID-19 vaccines.

Name	Vaccine Type	Primary Developers	Country of Origin	Authorization/Approval	Storage	Description
BNT162b2	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	UK, Bahrain, Canada, Mexico, US	−70 °C	BNT162b2 is a modified nucleoside mRNA-based vaccine developed by BioNTech and Pfizer. Fosun Pharma has licensed BNT162b2 in China. The vaccine is given as an intramuscular injection in two doses 21 days apart. BNT162b2 generates an immune response against SARS-CoV-2, the virus that causes COVID-19, by encoding a mutated form of the virus's full spike protein.
AstraZeneca/Oxford AZD1222	Adenovirus	The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India	The UK		2–8 °C	A safe and efficacious vaccine with more than 70% impact against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Mechanism: Replication-deficient viral vector vaccine (adenovirus from chimpanzees)
Sinovac CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China	2–8 °C	CoronaVac (formerly PiCoVacc) is a formalin-inactivated and alum-adjuvanted vaccine developed by the China-based biotechnology company Sinovac Biotech. The vaccine is administered in two doses 14 days apart.
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Russia	−18 °C	The Gamaleya Research Institute in Russia and Health Ministry of the Russian Federation evaluates their non-replicating viral vector vaccine, Sputnik V (formerly Gam-COVID-Vac), in a Phase 3 trial in Russia and internationally.
Moderna mRNA-1273	mRNA-based vaccine	Moderna	USA	the U.S. Food and Drug Administration's (FDA) has authorized the emergency use of mRNA-1273, Moderna's vaccine	2–8 °C	Moderna developed mRNA-1273 based on prior studies of related coronaviruses such as those that cause severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Moderna predicts it will be able to distribute 20 million doses to the United States in December 2020, and 100 m doses globally
Sinopharm BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, United Arab Emirates	2–8 °C	Sinopharm is developing a second inactivated COVID-19 vaccine candidate, BBIBP-CorV, with the Beijing Institute of Biological Products.

Table 8. Cont.

Name	Vaccine Type	Primary Developers	Country of Origin	Authorization/Approval	Storage	Description
Bharat Biotech BBV152	whole-virion β -propiolactone-inactivated	Bharat Biotech, the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV)	India	Bharat Biotech's 'COVAXIN TM ' by DCGI-CDSCO, MoH&FW	2–8 °C	COVAXIN is an inactivated vaccine obtained from the SARS-CoV-2 strain isolated at the NIV, Pune, an Indian virology research institute. The vaccine is used along with immune stimulants, commonly known as vaccine adjuvants (Alhydroxiqum-II), to improve immune response and longer-lasting immunity. The vaccine candidate is produced through the formulation of the inactivated virus with Kansas-based ViroVax's Alhydroxiqum-II adjuvant. COVAXIN mainly contains 6 μ g of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020-770), and the other inactive components such as 250 μ g aluminium hydroxide gel, 15 μ g TLR 7/8 agonist (imidazoquinolinone), 2.5 mg TM 2-phenoxyethanol, and phosphate buffer saline up to 0.5 mL.
Johnson and Johnson vaccine (JNJ-78436735)	Viral vector	Janssen Pharmaceuticals Companies of Johnson & Johnson	USA	Johnson & Johnson COVID-19 Vaccine Authorized by U.S. FDA for Emergency Use	2–8 °C	The J&J/Janssen vaccine was 66.3% effective in clinical trials (efficacy) at preventing laboratory-confirmed COVID-19 illness in people who had no evidence of prior infection 2 weeks after receiving the vaccine. People had the most protection 2 weeks after getting vaccinated. The vaccine had high efficacy at preventing hospitalization and death in people who did get sick. No one who got COVID-19 at least 4 weeks after receiving the J&J/Janssen vaccine had to be hospitalized.

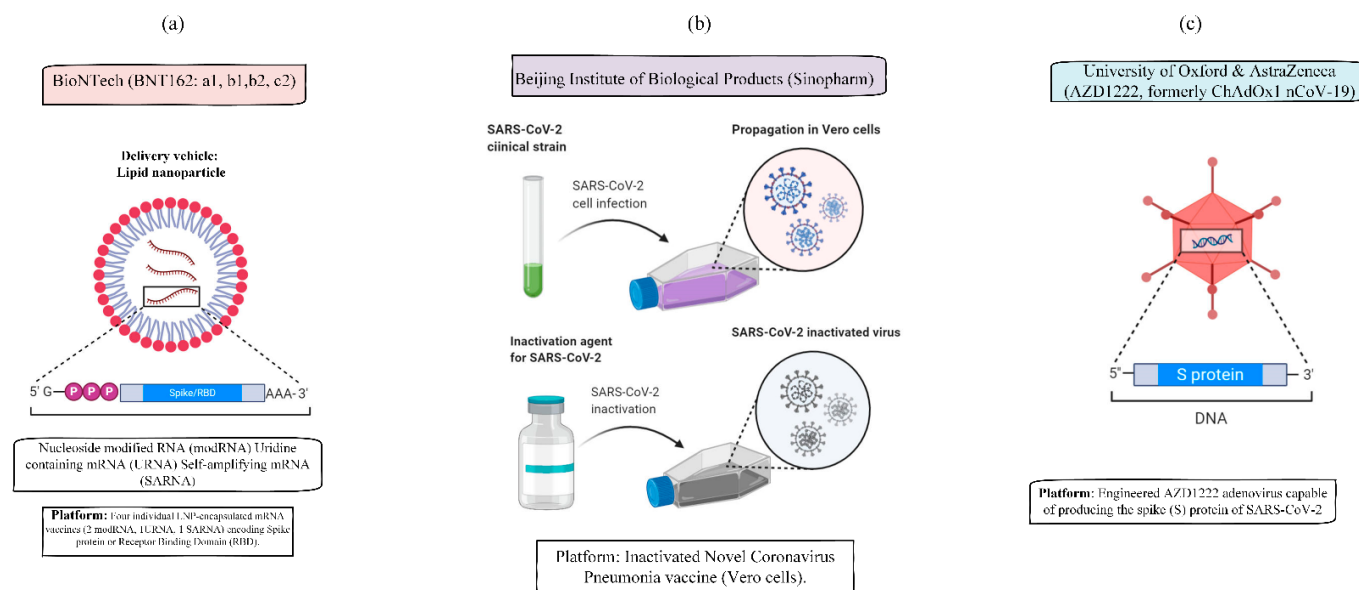


Figure 15. The mechanism and type of process of the approved (a) BNT162b2, (b) Sinopharm and (c) Oxford/AstraZeneca vaccine (Reprinted from “Clinical Phase Vaccine Candidates for COVID-19”, by BioRender.com, accessed on 15 April 2020) [214].

11. The Effect of COVID-19 on Pregnant Women

Due to the complications of COVID-19, pregnant women are expected to be at risk of developing severe COVID-19 compared to non-pregnant women. It should be noted that the easy spread of viral respiratory diseases, such as influenza, during pregnancy indicates that pregnant women are more vulnerable to COVID-19 and require more medical care [215,216]. Generally, mechanical and physiological changes in pregnancy gained susceptibility to COVID-19, significantly when it affects cardiorespiratory and graviora, and it increases the rate of progression in respiratory failure. Due to physiological changes in the immune and cardiopulmonary system in pregnant women (e.g., improved diaphragm, increased oxygen consumption and respiratory mucosal oedema), they are very susceptible to respiratory pathogens severe pneumonia [217]. Additionally, pregnant people with COVID-19 might be at increased risk of adverse pregnancy outcomes, such as preterm births. Figure 16 demonstrates an overview of pregnant women with COVID-19 disease in diagnosis, prevention, and potential treatments.

A wide range of vaccines is routinely and safely administered during pregnancy. As mentioned in the vaccine section, Pfizer-BioNTech vaccines are an effective vaccine against COVID-19. However, as clinical trials of the COVID-19 vaccine in pregnant women have not yet been performed, there is insufficient evidence to recommend routine use of the COVID-19 vaccine to pregnant women. However, given the mechanism and function of these vaccines (mRNA vaccine), experts believe that it is unlikely to pose a risk to pregnant women. Moreover, mRNA vaccines are not expected to pose a risk to the breastfed infant. It should be noted that mRNA vaccines do not contain a live virus that causes COVID-19 and therefore, cannot give a person COVID-19. In addition, mRNA vaccines do not interact with genetic DNA because mRNA does not enter the cell nucleus. However, the potential risks of mRNA vaccines for pregnant women and their fetus are unknown because they have not been studied in pregnant women. According to the CDC recommendation, Acetaminophen may be offered as an option for pregnant women experiencing other post-vaccination symptoms as well [218].

Diagnostics of COVID-19

Pregnant Women

- ☐ Computed Tomography (CT) scans
- ☐ The Reverse Transcription Polymerase Chain Reaction (RT-PCR)
- ☐ Serological test

Symptoms

- ☐ Shortness
- ☐ Difficulty in breathing (dyspnea)
- ☐ Chest pain
- ☐ Lung parenchymal alteration

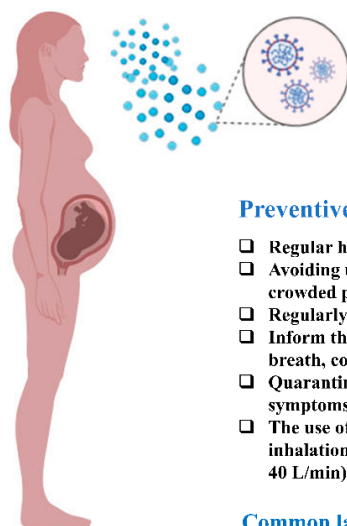
Management of COVID-19 During Pregnancy

- ☐ Isolation of pregnant women suspected of having COVID-19 from other patients and maintain in hospitalization equipped with appropriate health services and professionally trained physicians

Classification of pregnant women

- ☐ Moderate illness (i.e. symptomatic with healthy vital signs)
- ☐ Extreme disease (i.e. respiration rate approximately 30/min, saturated O₂ resting approximately 93%, partial blood oxygen/oxygen concentration approximately 300 mmHg)
- ☐ Critical disease (i.e. organ failure shock, respiratory failure requiring mechanical ventilation, or refractory hypoxemia requiring oxygenation of the extracorporeal membrane).

SARS-CoV-2 (COVID-19 virus)



Medication to COVID-19 for Pregnant Patients

The antiviral drugs

- ☐ Atomized inhalation of interferon-ALPHA
- ☐ Oseltamivir
- ☐ Lopinavir
- ☐ Ritonavir
- ☐ Ganciclovir
- ☐ Arbidol

The use of antibiotics to treat secondary bacterial pneumonia

- ☐ Beta-lactam (Abipenem and sulbactam sodium),
- ☐ Cephalosporins (cefoperazone sodium and ceftazidime),
- ☐ Macrolides (azithromycin)
- ☐ Quinolones (moxifloxacin)

Preventive Measures During Pregnancy

- ☐ Regular hand washing
- ☐ Avoiding unnecessary outdoor activities, infected individuals, crowded places, and public gatherings
- ☐ Regularly check their temperature
- ☐ Inform their doctors immediately if they experience shortness of breath, cough, or fever
- ☐ Quarantine for 14 days (woman with a travel history of COVID-19 symptoms)
- ☐ The use of Extracorporeal oxygenation of the membrane and inhalation of oxygen (60%–100% concentration with a flow rate of 40 L/min) (hypoxia)

Common laboratory findings

- ☐ Lymphopenia (lymphocyte amounts smaller than average in the blood)
- ☐ Elevated C-reactive protein (inflammatory indicator)
- ☐ increased Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)

Figure 16. An overview of pregnant women with COVID-19 disease in terms of diagnosis, prevention, and potential treatments.

There is no evidence of neonates infection in women who have given vaginal birth. To understand the risk of infection, further studies are required, and guidelines should be taken for the method and timing of delivery in pregnant women with COVID-19 infection. The previous investigations on the severe acute respiratory syndrome (SARS) virus have represented that the virus can cause intrauterine fetal demise, premature birth, and intrauterine growth limitation; hence, testing suspected cases and continuous control of the patients their infants is importantly necessary [219,220]. Additionally, there is no evidence of mother-to-child transmission risk through cesarean and delivery section [221]. Table 9 summarizes the published articles on the relationship between pregnancy and COVID-19.

Table 9. A summary of published research on pregnant women with COVID-19.

Title	Objective	Description
❖ Coronavirus Disease 2019 (COVID-19) During Pregnancy: A Case Series [222]	➢ Determination of the clinical characteristics of COVID-19 in pregnancy and their newborn infant. ➢ Evaluation of transmission of SARS-CoV-2 virus vertically through the intrauterine.	• A case study in obstetrics and gynecology ward of Tongji Hospital (Huazhong University of Science and Technology, Wuhan, China). • Evaluation of demographic, clinical, laboratory and radiological characteristics of SARS-CoV-2 infection series. • Sampling: oropharyngeal swab, placenta tissue, vaginal mucus, and breast milk of mothers and oropharyngeal swab, umbilical cord blood, and serum of newborns.
❖ Coronavirus disease 2019 in pregnant women: a report based on 116 cases [223]	➢ Clinical characteristics of SARS-CoV-2 infection. ➢ Vertical transmission potential of SARS-CoV-2infection.	• Sampling: amniotic fluid, cord blood, and neonatal pharyngeal swab. • Clinical evaluation of 116 pregnant women with coronavirus pneumonia. • The most common symptoms: fever (50.9%), cough (28.4%); patients presented without symptoms (23.3%). • Severe pneumonia (6.9%). • Preterm delivery (21.2%). • Negative newborns (86%).

Table 9. Cont.

Title	Objective	Description
❖ Coronavirus disease 2019 (COVID-19) pandemic and pregnancy [217]	➤ A comprehensive study of the effects of COVID-19 on pregnant women and their infants.	• comprehension of pathophysiology and susceptibility. • Diagnostic challenges with real-time reverse transcription-polymerase chain reaction (RT-PCR). • Therapeutic controversies. • Intrauterine transmission. • Maternal-fetal complications. • Antiviral therapy and vaccine development.
❖ A Review on the Effect of COVID-19 in Pregnant Women [224]	➤ Evaluation of COVID-19 and its severity in pregnant women and its comparison with SARS and MERS.	• The priority of caring for pregnant women with physiological conditions of immunodeficiency in a higher-level health center. • Treatment and maintenance of pregnant women in the prenatal, postpartum or postpartum period, in an isolated environment or negative pressure. • Attempts to prevent mother-to-child transmission of SARS-CoV-2 or iatrogenic infection during and after delivery. • Separation of infants from the mother of COVID-19 after postnatal stage. • Need to read more about breastfeeding health of mothers with COVID-19.
❖ Maternal and Neonatal Outcomes of Pregnant Women With Coronavirus Disease 2019 (COVID-19) Pneumonia: A Case-Control Study [225]	➤ A case-control study to compare clinical characteristics and maternal and neonatal outcomes of pregnant women with and without COVID-19 pneumonia.	• The study conducted on 16 pregnant women with COVID-19 and 18 pregnant women suspected of COVID-19. • Vaginal delivery (2), Cesarean delivery (32). • Having symptoms of fever and cough at the time of admission, the presence of symptoms of COVID-19 pneumonia in their CT scan. • Lower counts of white blood cells (WBCs), neutrophils, C-reactive protein (CRP), and alanine aminotransferase on admission (Patients with COVID-19 pneumonia). • Increase the levels of WBCs, neutrophils, eosinophils, and CRP in postpartum blood tests of pneumonia patients. • No COVID-19 infection in infants.
❖ Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records [226]	➤ Evaluation of clinical features of COVID-19 in pregnancy and the potential for vertical intrauterine transmission of COVID-19 infection.	• Evaluation of clinical records, laboratory results and chest CT scan of 9 pregnant women with COVID-19 pneumonia. • Cesarean delivery. • Observed symptoms: fever, cough, myalgia, sore throat and lethargy. • Fetal distress control in two cases. • Observation of lymphopenia in five patients ($<1.0 \times 10^9$ cells per L). • Increased aminotransferase concentration in three patients. • No observation of neonatal asphyxia in infants.
❖ An Experimental Model for Peri-conceptual COVID-19 Pregnancy Loss and Proposed Interventions to Optimize Outcomes [227]	➤ Report an experimental model for COVID-19 infection loss and suggest interventions to optimize outcomes.	• Such a model has classified lesions as permissive at term, but catastrophic early first-trimester pregnancy or near embryo implantation. • To resolve this challenge, recurrent pregnancy loss suggests workable interventions utilizing clinical experience, but success strongly depends upon accurate and prompt SARS-CoV-2 recognition. However, this experimental model can warrant a high-risk determination for such cases, the patients should be received priority access to treatment and screening resources.

Table 9. Cont.

Title	Objective	Description
❖ Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth [228]	➤ A complete study of three pregnant women with COVID-19 in Renmin Hospital.	• Swab sampling from all three patients using qRT-PCR. • Vaginal delivery. • One case of premature birth.

12. Conclusions

The prevalence of COVID-19 has recently been identified as a global health emergency. According to the WHO, ~131M people have been infected, of which ~74.4M have recovered, and unfortunately, more than ~3M people have died so far. Quarantine alone is not enough to prevent the outbreak of COVID-19, and the global impact of this viral infection on the economy is a significant concern. Although researchers are trying to find an utterly effective drug for the definitive treatment of COVID-19, no 100% effective drug has been discovered for complete recovery. Fortunately, due to researchers and pharmaceutical companies' efforts, many effective vaccines to prevent the prevalence of this deadly disease have been approved by the World Health Organization. However, it takes a long time for these effective vaccines to reach all the world's people and all people to be vaccinated. Until then, all the points recommended by the World Organization to prevent the prevalence of this disease must be fully observed.

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