P- ISSN 1991-8941 E-ISSN 2706-6703
2025,(19), (01):58 – 78

Journal of University of Anbar for Pure Science (JUAPS)

Open Access

SARS-CoV-2 history, diagnosis, genetic diversity, and treatment : a comprehensive review

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ARTICLE INFO

Received: 01 / 05 /2024
Accepted: 01/ 10 /2024
Available online: 14/ 06 /2025

DOI: 10.37652/juaps.2024.149325.1247

Keywords:
COVID–19, Diagnosis, Treatment, Mutated viruses, Coronavirus emergence.

ABSTRACT

This article comprehensively examines the history, diagnosis, genetics, diversity, and treatment of SARS-CoV-2. It details the emergence of coronaviruses over the past 50 years, including the coronavirus from 2019 and its subsequent mutations, along with updated information about this virus. This review explains the development and nomenclature of coronaviruses, their cellular invasion through glycoprotein spikes binding to ACE-2 receptors, and the mechanism of cell entry via endocytosis. Diagnosis methods for COVID-19, including nucleic acid amplification, serology, and imaging techniques like chest X-ray and CT scan tests, are discussed. Treatment approaches for COVID-19 are outlined, emphasizing healthcare, antiviral medications like Remdesivir, immunotherapy using convalescent plasma, and adjuvant therapies such as anticoagulants and vitamins. Moreover, this review includes mutated coronaviruses, such as the Delta variant and the Omicron variant, and their influence on vaccine efficacy. This review covers the characteristics and impact of variants such as B.1.1.7, B. 1.35.1, P.1, Delta, Delta plus, and Omicron, addressing their mutations that affect virus transmission and vaccine efficacy, with a brief overview of four WHO-approved vaccines and their effectiveness against potential new variants.

Emergence of coronaviruses

Recent research indicates that extended COVID-19 is becoming less of a threat over time [1]. However, experts advise that caution remains warranted [2]. For almost 50 years until the present, the majority of individuals have not heard of coronaviruses; nonetheless, the various forms of these viruses have been identified. In 1931, acute bronchitis of newborn fowl was identified by Schalk and Hawn [3] and by Bushnell and Brandly [4]. In subsequent years, researchers conducted numerous studies on mice and birds to confirm the validity of infection with this virus, identifying two strains exhibiting immunity and isolating the virus. In 1967, Tyrrell and June [5] of the Medical Microbiology Laboratory of the College of Medicine at St Thomas' Hospital in London, identified three respiratory viruses, two of which were previously responsible for human diseases, namely, E229 and B814, and published their images taken with an electron microscope so that these viruses can be distinguished from other viruses (Almeida, et al., 1967). They found particles responsible for infectious bronchitis in birds. In 1968, Almeida and

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Tyrrell noted the presence of some viruses that cause bronchitis in birds, alongside those causing respiratory and liver diseases (Table 1).

Table 1. Detailed characteristics of coronaviruses according to a publication published in the Journal of Nature (220 (5168):650) 1968 by David. T at the (CCCR) Common Cold Centre Research, in collaboration with Salisbury Wiltshire, with a short bibliography containing relevant data.

Characteristics of the viruses			
	Human strains	**Mouse hepatitis**	**Avian infectious bronchitis**
Girth filtration	**89 µm**	**80–120 µm**	
Electron microscopy	**80 – 100 µm**	**100 µm**	**80–120 µm**
Characteristic of the structure surface	+	+	+
The ether liability (Essential Lipids)	+	+	+
Ribonucleic Acid content and insusceptibility to DNA inhibitors	+	+	+
Infectious unit of density	**1.19**	**?**	**1.18**
Repeating of cytoplasmic vesicle	+	+	+
Included the diameter of particles by using negative-contrast technique projections			

In 1968 [6], under the general heading of News and Viruses, the term coronaviruses was first documented, classifying avian bronchial viruses as gamma viruses, whereas beta coronaviruses are considered viruses that infect humans. The human type (HCoV-229E) virus identified by Almaida and Tyrrell is an alpha coronavirus. In 2019, it initially appeared in Wuhan, China. The virus was first known as 2019-nCoV, but the WHO later changed the designation to COVID-19 [7]. The virus is a member of the vast class of viruses known as B-type coronaviruses, which are widely distributed and have been linked to two earlier epidemics: SARS-CoV-2 in China in 2002 [8] and Middle East respiratory disease (MERS)-CoV in the Middle East in 2012 [9]. In the field of coronaviruses, the first virus named coronavirus appeared, which infected humans under the name E229, O C43, leading to the occurrence of minor infections such as the common cold [10]. This was succeeded by the outbreak and emergence of severe acute respiratory syndrome (SARS), followed by the emergence of Middle East respiratory syndrome (MERS), also known as camel flu, which caused severe infections. The transmission of these infections may have originated from bats, camels, or civet cats.

This review also addresses SARS-CoV-2, its structure, invasion mechanisms, imaging techniques, treatment options, variants, spike mutations, immune evasion, ongoing research on virus mutations, vaccine effectiveness, and updated information.

Name of viruses as coronaviruses:

In 1968, the Nature Journal clarified that these viruses were previously a group of unrecognized members that scientists called coronaviruses. They were identified via electron microscopy, revealing a halo-like appearance, which holds various implications. Scientists used the sun as a model when naming coronaviruses and comparing them with the projections on the virus' outer surface resembling the solar corona. They also disregarded the suggestion from certain scientists about the presence of points on the crown, as shown in Image 1.

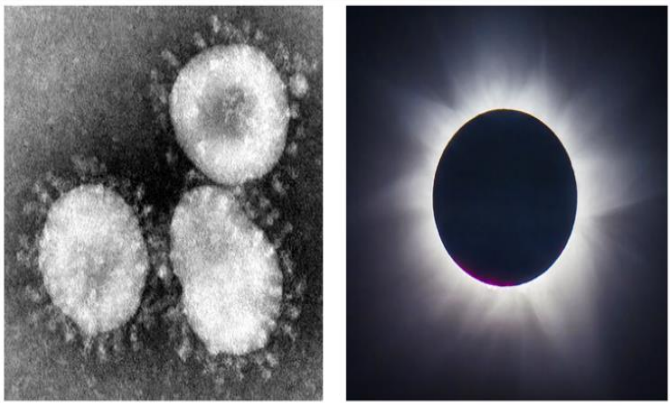

Image 1. Left: The external host cell exhibiting the virus structure, comprising a core of DNA or RNA encased in a capsid (coronaviruses). Right: The coronavirus's analogy to the sun's fascination during an eclipse.

Description of coronaviruses and how they invade cells

Viruses RNA are single-stranded coronaviruses with a diameter of 120 nm, capable of recombination and mutation, resulting in many variants. About 40 different types of viruses exist. The similarity in the appearance of these viruses to coronaviruses is due to the high prevalence of glycoproteins and the presence of peplomers that facilitate viral entry into the host. The

spike contains two subunits: the first subunit S1 binds to the surface of the host, and the second subunit S2 facilitates fusion with the cell membrane, functioning as a receptor for SARS-CoV-2 or SARS-CoV-1, which corresponds to angiotensin-converting enzyme 2 (ACE-2). It differs from the enzyme blocked by ACE-1, which serves as a disincentive, such as enalapril and ramipril. In summary, a link between the spike subunit S1 and the enzyme ACE-2 will be established on the cell surface, thereby activating the serine protease via the host membrane, where the spike interacts with TMPRSS2 and initiates ACE-2. TMPRSS2 activate the S2 subunit, facilitating the fusion of the cell membrane with the virus, allowing the virus to enter the cell. Once inside, the virus begins to release endosomes through acidification or by utilizing cysteine, protease, and cathepsin, as depicted in Figure 2 [11].

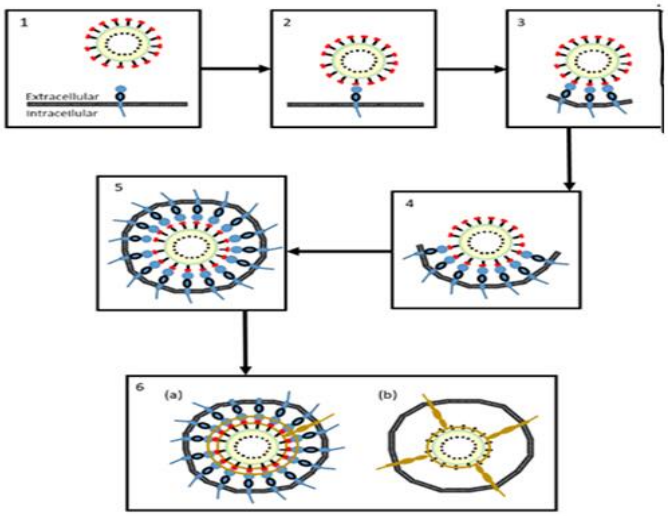

Figure 2. Mechanics of coronavirus (SARS-CoV-2–2) inside cells.

Step (1): As the coronavirus approaches the cell membrane. Step (2): The red color representing the subunit S1 is associated with the leg end of the glycoprotein spike of the virus, whereas the blue molecule represents ACE2. Step (3): The membrane forms an envelope surrounding the virus and an endosome. Step (4): The process continues. Step (5): The endosome will be completed. Step (6): The virus can enter the cell using two methods: First, serine protease binds with the cell membrane (depicted in brown; TMPRSS2), followed by the cleavage of the virus subunits S1 (red) occurs from their units. S2 (black) and cleavage also occur in enzymes (ACE-2), after which the endosome enters the endocytosis cell [12]. Subsequently, the virus is removed by acidification or by the action of another protease, such as cathepsin. The second method involves the same serine protease that induces irreversible morphological changes to the virus subunit S2, thereby activating, followed by the fusion of the virus with the cell membrane to facilitate cellular absorption [13,14]. Figure 3 illustrates the cyclical nature of COVID-19 [15].

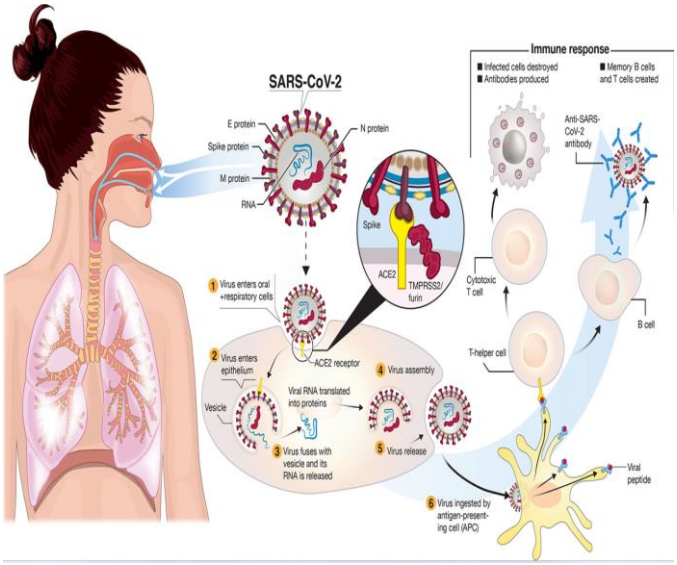

Figure 3. Life cycle and transmission of SARS-CoV-2, which causes COVID-19.

Diagnosis of COVID-19

Accurate diagnosis relies on the imaging findings and assessment of patients with possible SARS-CoV-2 infection or different high-risk stages of COVID-19, in conjunction with symptoms and laboratory criteria, which culminate in different clinical outcomes [16,17].

(A) Tests of viral detection - Nucleic acid amplification test (NAAT) (molecular testing)-Antigen testing.

The tests of both antigens are most effective when the viral load is high; they may also be used in diagnostic scenarios where the individual has a confirmed exposure to COVID-19. Currently, the majority of global cases worldwide are confirmed by NAATs.

Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) is the most reliable and rapid technique for viral RNA detection. It is based on the clinically validated results and provides high-throughput

results within a few hours [18]. The RT-PCR method is regarded as the gold standard for detecting the presence of SARS-CoV-2 due to its specificity in measuring RNA viruses, as opposed to secondary biomarkers such as antibodies or antigens [19]. The RT-PCR method depends on two sequential reactions.

a) Reverse Transcription: The viral RNA is initially extracted and then reverse transcribed. This process is followed by the synthesis of complementary DNA (cDNA), which requires (a) the use of a reverse transcriptase enzyme and (b) amplification of cDNA, achieved through PCR employing gene-specific primers and fluorescent hydrolysis probes. Two RT-PCR assays are used to identify SARS-CoV-2. The initial phase, termed amplification, incorporates reverse transcriptase enzymes and two to three primer sets with sequences specific to designated regions of the viral genome. In addition, internal control reagents and positive and negative reagents are used. The first step involves the preparation of RT-PCR templates from DNA, which are used in the second step, resulting in an amplification of DNA copies by multiple thermal cycles. The second reaction involves amplification occurring in a selected genomic region, driven by gene-specific primers, while probes generate fluorescent signals concurrently with the amplification at these gene regions, rendering the reaction system quantifiable [20]. The control samples are processed similarly to the patient samples, where each panel yields reliable results with minimal false positives/negatives, as well as a high degree of confidence, while accounting for potential failures in the reagent or experimental process. The test is conducted on lower and upper respiratory specimens, including lower and upper respiratory tract specimens, oropharyngeal and nasopharyngeal samples, bronchoalveolar lavage, nasal swabs, throat swabs, and saliva [21,22]. The following steps of the RT-PCR test are depicted in Figure 4.

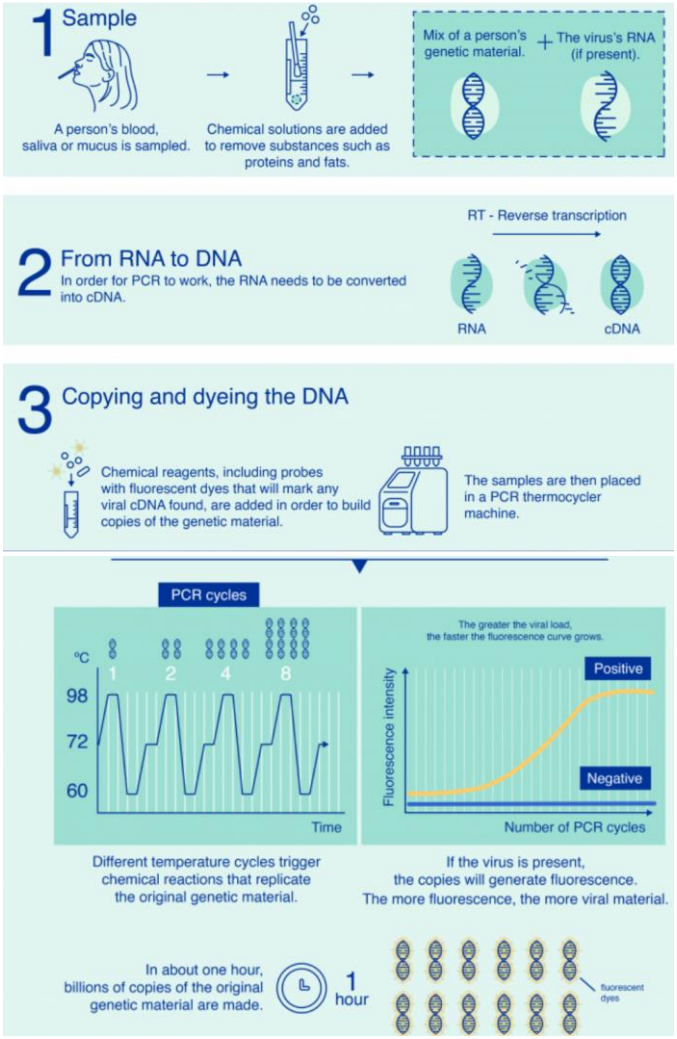

Figure 4. Mechanism of COVID-19 testing via real-time RT-PCR.

The analysis or the positive result of the virus does not provide adequate clarity regarding the presence of an infectious agent, as viruses, regardless of their viability, are required for transmission. This does not include the parts identified by the previous study [23], and due to the gradual degradation of inactivated viruses over time, detection may persist for several weeks posts-infection, resulting in the imposition of restrictions on individuals who do not pose an infection risk [24]. Individuals with a high cycle threshold are unlikely to face infection risk. Research indicates that the cycle limit values in samples derived from live viral cultures are considerably low, with high log copies associated with them. Thus, the accuracy of the results depends on several factors, including the sampling location, disease stage, transmission rate, and extent of virus reproduction or clearance [25].

(B) Antibody detection (serology tests) For individuals undergoing testing and previously infected without exhibiting symptoms, the infection can be determined through antibody tests. These tests use purified SARS-CoV-2 proteins, not live viruses, and can be conducted in Class II Biosafety Cabinets. The immune system produces antibodies (IgM and IgG) in response to SARS-CoV-2. The diagnosis of the presence of the virus is conducted indirectly via serological tests, which detect antibodies or immune system particles [26]. Within 2 weeks, these bodies are produced after removing the virus from the system. In general, the percentage of the infected population and how many of them have acquired immunity against the virus can be determined [27].

Thus, serologic tests can determine whether an individual has previously contracted COVID-19. Furthermore, these tests are crucial for herd immunity screening, surveillance, and epidemiologic studies, such as understanding the transmission dynamics of the virus in the general population. Serology cannot be used for acute SARS-CoV-2 infections as a standalone diagnostic test. However, it may be useful in different settings such as negative NAAT results and the diagnosis of patients with delayed presentation or prolonged symptoms [28,29]. Serological test results can help identify individuals previously infected with the virus, revealing those who have developed protective antibodies. Such data can be used to screen plasma donors and treat critically ill patients suffering from COVID-19 [30,31,32].

A double serum sample can be obtained, according to the recommendations of the WHO; the first serum represents the acute case, and the second is after the convalescence stage, which ranges between 2 and 4 weeks [33]. In instances where an increase in antibody levels or seroconversion aids in confirming whether the infection is recent or acute, researchers may also determine if the initial sample is positive due to a previous infection unrelated to the current disease. Moreover, patients with severe illness exhibit faster seroconversion than those with asymptomatic infections or mild illness [34].

Tests that detect antibodies fall into two categories:

Point-of-care (POC) assays are lateral flow devices that detect IgG, IgM, IgG, or total antibodies in plasma, serum, full blood, and/or saliva. A feature of some POC assays utilizing full blood is that they can be performed using blood specimens obtained via fingerstick instead of venepuncture [35]. In the POC test, antibodies fixed to a membrane are used to detect the molecule(s) of interest (presence of specified antibodies on patient's blood specimen). An assay consists of a cassette containing a polymer membrane strip, which normally features two lines: an assay line and a control line. The patient sample is deposited via a port onto the sample pad and passes through the strip by capillary motion [36].

If the test is positive, the test and control lines will be visible; however, if the test is negative, only the control line will be displayed. The second category comprises enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay (CIA). ELISA is a solid-phase enzyme immunoassay in which recombinant virus antigen is coated as a target molecule on the surfaces of plastic wells. A serum sample from the patient is applied to the well. If antibodies (IgG or IgM) are present in the sample, they will bind to the target antigen. The whole unbound substrate is removed by washing the surplus sample multiple times, after which a second solution is added by introducing human-labeled secondary antibodies and allowed to bind; no binding occurs in the absence of the specific antibody on the specimen. The surplus is eliminated through washing, and the binding of target antibodies is verified through a color-changing reaction that is enzyme-dependent (usually horseradish peroxidase). The spectrometer measures the color change, allowing for the determination of the condensation from the target antibody. In chemiluminescent immunoassays, binding of secondary antibodies is assured through different chemiluminescent substrates [37].

(C) Imaging

This technique plays a key role in the diagnosis process, management, and follow-up of injuries associated with suspected pneumonia, and it involves the following:

Chest X-ray

In the early stages of COVID-19 infection, chest X-rays exhibit low sensitivity in identifying early pulmonary changes. However, they may appear completely negative in the advanced stages of the infection. Analysis of chest X-ray can reveal bifocal alveolar opacities, which tend to converge to form complete opacification of the lung [38, 39,40].

Chest computed tomography (CT)

CT scan includes a series of scans on the patient's chest from various angles to produce cross-sectional images, which are distinct and based on a phase of infection following the onset of symptoms [41,42]. Multifocal bilateral ground-glass opacities associated with zones of consolidation exhibiting circumferential, asymmetrical, and posterior distribution and absent pleural effusions are characteristic of early SARS-CoV2 infection (symptomatic individuals) [43,44]. As the disease progresses, subpleural control, mad paving (lobular septal intensification for variable alveolar filling), and consolidation may become apparent [45,46]. Figure 5 shows a chest CT image of a 34-year-old female patient with COVID-19 disease [47].

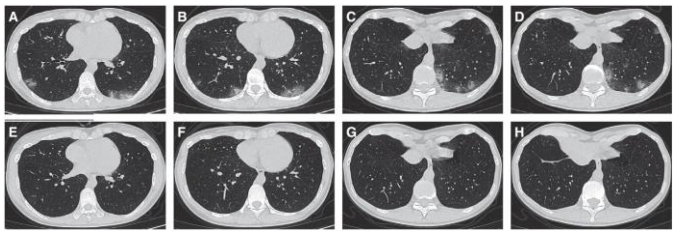

Figure 5 CT scans from a 34-year-old female patient with COVID-19 disease (A–D) Chest CT scans at admission. (E–H) Chest CT scans 4 weeks after discharge show near recovery from multiple patchy ground-glass opacities in the lower lobes, consolidations, and bronchiectasis.

A CT scan can aid in diagnosing COVID-19 in individuals with high clinical uncertainty from infection, even in the early stages (more sensitive than an X-ray) but is not recommended for routine screening [48,49]. It is rapid and sensitive and has been tentatively utilized as a clinical diagnosis tool for COVID-19 at the onset of disease outbreak due to the incorrect negative rate associated with RT-PCR [50]. NAATs are more appropriate for accurate diagnosis compared with syndromic testing and CT scanning, as they may immediately target and diagnose specific pathogens [51].

Lung ultrasound

Lung ultrasonography is utilized as a diagnostic tool in certain facilities as an alternative to chest X-rays and CT scans [52]. It has features such as portability, bedside assessment, ease of sterilization, absence of radiation exposure, repeatability during follow-up, and availability in resource-limited settings. Moreover, it may be used in pregnant women and children [53,54]. The prevalent trend in patients with COVID-19 is the presence of B lines (long wide vertical bands of hyperechoic coalescent artefacts originating from the pleural line, indicative of interlobular septal edema). Other findings contain consolidations, perilesional pleural effusion, and pleural thickening. Although the findings are not exclusive to COVID-19, they significantly enhance the likelihood of illness in relation to a characteristic clinical presentation [55].

COVID-19 treatment

The studies demonstrate the absence of a specific, effective treatment for COVID-19. Thus, COVID-19 management focuses on supportive care, including the treatment of symptoms and the prevention of complications [56].

The pathogenesis of COVID-19 is believed to be driven by two main mechanisms. Early in the course from infection, SARS-CoV-2 replication is the main catalyst of the disease. Tissue damage results from a virus that induces disease via an exaggerated immune/inflammatory response, leading to infection or disease transmission. Antiviral therapy is anticipated to have a greater effect early in the disease progression than during the late stages, whereas immunosuppressive/anti-inflammatory therapy is likely to be more beneficial in later stages of COVID-19 [57].

Supportive therapy

It primarily seeks to alleviate the signs and symptoms for the comfort and well-being of the patient, but it can also effectively reduce the sequelae of the disease.

Symptomatic relief

The WHO recommends that patients with moderate COVID-19 be given symptomatic therapy for fever, body aches, and coughs, such as antipyretics

(paracetamol or nonsteroidal anti-inflammatory drugs such as ibuprofen) and adequate nutrition. Patients are advised to avoid laying on their back, as this renders coughing ineffective [58]. The use of honey and antitussives reduces the frequency and severity of coughing [59, 60].

Fluid replacement

To replace and replenish lost body fluids due to bleeding, perspiration, or other pathological processes, doctors recommend medical intervention for replenishment. This procedure aims to correct any metabolic or electrolyte imbalances, including metabolic acidosis or hyperglycaemia [61].

Oxygen support

The most common symptom of severe COVID-19 disease is shortness of breath, which is often accompanied by hypoxemia. The disease appears most severe about 1 week after the onset of symptoms. Therefore, oxygen must be given to patients who are severely ill, while monitoring the status of the respiratory system, as some patients may progress to severe respiratory distress syndrome (ARDS) [62].

Prone positioning

Proning involves positioning patients in a prone orientation, laying on their stomachs. This is utilized in therapy for patients requiring artificial ventilation under stringent conditions for moderate-to-severe ARDS to improve their respiration [63,64]. It is also utilized by patients with oxygen masks and continuous positive airway pressure as an alternative to ventilation during the COVID-19 pandemic [65].

Antiviral therapy

Following the replication of SARS-CoV-2 and its clinical symptoms in COVID-19, antiviral treatments have become a significant component of COVID-19 therapy. Transmembrane serine 2 protein, angiotensin-converting enzyme 2 (ACE2) receptor or endocytosis, viral membrane fusion, SARS-CoV-2 3-chymotrypsin-like protease, and RNA polymerase all inhibit drug entry into the virus [66]. Given that viral replication occurs early in the course of COVID-19, antiviral treatment can have a greater effect before the disease advances into the hyperinflammatory state at later phases of the disease, which can result in critical illness [67]. Antiviral drugs include but are not limited to remdesivir, lopinavir/ritonavir, umifenovir, and favipiravir. Understanding the current targets and discovering new possible therapeutic targets are crucial for the development of effective vaccines and antiviral drugs against the current SARS-CoV-2 outbreak and possible future outbreaks [68].

Remdesivir

The only drug currently approved to treat COVID-19 by the Food and Drug Administration (FDA) is remdesivir, an antiviral agent. Additional oxygen is recommended for hospitalized patients under remdesivir treatment [69]. Remdesivir is an intravenous adenosine analogue. It binds to viral RNA polymerase, preventing viral reproduction via the early terminus of RNA transcription. It demonstrates efficacy in vivo and in vitro against SARS-CoV-2 [70, 71].

Lopinavir/Ritonavir

This is a fixed-dose combination antiretroviral oral medication used for the treatment and prevention of HIV/AIDS [72]. In vitro, lopinavir/ritonavir inhibits SARS-CoV 3-chymotrypsin-like protease, which plays a role in viral replication. It is believed to have a poor selectivity indicator, suggesting the need for elevated medical scales to investigate in vivo suppression [73,74]. Lopinavir/ritonavir's adverse effects include queasiness, vomiting, diarrhea (common), and hepatotoxicity [75]. The National Institutes of Health recommends against the use of lopinavir/ritonavir for COVID-19 treatment, except within the context of a clinical trial [76].

Chloroquine or hydroxychloroquine

Hydroxychloroquine is an analogue of chloroquine, an oral antimalarial drug. In addition to malaria, hydroxychloroquine is utilized to treat autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis. In vitro studies have shown that hydroxychloroamine and chloroquine may prevent the transmission of SARS-CoV-2 to endosomes via early endosomes. Thus, inhibiting the fusion of the virus with the host and cell membranes [77,78] may prevent the release of the viral genome [79].

Ivermectin

Ivermectin is an oral antiparasitic drug used in the treatment of several careless equatorial illnesses, including onchocerciasis, helminthiases, and scabies [80]. Furthermore, it can reduce the transmission rate of malaria by eliminating mosquitoes that feed on treated people and cattle [81]. Ivermectin inhibit host import by nuclear messenger proteins alpha-beta-1, a mechanism that constitutes a remarkable intracellular transmission strategy exploited by viruses to dampen the antiviral response and promote infection [82]. Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in vitro [83].

Immunotherapy

Given the hyperactive inflammatory effects of SARS-CoV-2, immune response-modulating agents have been investigated as therapies for moderate to critical COVID-19 management [84]. Such agents contain the following.

a- Blood-derived product:

Human blood-derived products are acquired from people who have recovered from SARS-CoV-2 (e.g., convalescence plasma and immunoglobulin products) [85,86]. These products are assumed to possess acute antiviral characteristics, such as convalescence plasma, as well as/or immunomodulatory effects similar to those observed in mesenchymal trunk cells [87].

Convalescent plasma: Donors who have recovered from COVID-19 and whose bodies possess plasma with SARS-CoV-2 antibodies can help combat the virus and alter the inflammatory response of the infected individual [88].

Mesenchymal stem cells: Multipotent adult trunk cells called mesenchymal trunk cells are found in the tissues of humans, including the umbilical cord. The stem cells may self-renew during division and differentiate into multiple cell types, including chondroblasts, hepatocytes, osteoblasts, and adipocytes, which has prompted clinical research into regenerative drug. Mesenchymal trunk cells may decrease serious lung injury and prevent cell-mediated inflammatory responses induced through SARS-CoV-2. Moreover, the absence of ACE2 receptors in mesenchymal stem cells exploited by SARS-CoV-2 for cellular entry renders these cells resistant to infection [89,90].

b. Immunomodulators

Patients with severe COVID-19 are characterized by the presence of attackers and the unregulated release of pro-inflammatory cytokines, known as cytokine storms, which are common critical contributors to COVID-19 pathogenesis [91]. This results in fatal acute lung injury and ARDS. Thus, exploring anti-inflammatory treatments may be the optimal strategy for a significant reduction in COVID-19 mortality [92]. Agents in this group include corticosteroids [93], which can mitigate systemic inflammation, as well as most targeted anti-inflammatory therapies such as interleukin inhibitors [94,95], interferons [96], and kinase inhibitors [97].

Corticosteroids: These robust medications include glucocorticoids such as dexamethasone, methylprednisolone, prednisone, and hydrocortisone [98]. The strong properties of these drugs, such as corticosteroids, are instrumental in assessing the extent of the response to infections, particularly lung infections, as well as in managing the multi-organ dysfunction observed in patients with severe COVID-19. A multicenter, randomized clinical experiment on hospitalized patients for COVID-19 found that mortality rates are lower in patients receiving dexamethasone compared with those who satisfied the criteria for withdrawal from care [99].

Interferon (alpha and beta): These agents are used as potential drug therapy for COVID-19 and are classified as drugs with antiviral properties in vitro and in vivo. Studies have shown no benefit of interferon for patients with other coronavirus infections (such as MERS and SARS). Additionally, interferons have important toxicities that outweigh the potential benefits. Interferon usage in the early stages of the disease maty result in negative effects, as there is insufficient evidence from the National Institutes of Health [100].

Interleukin-1 inhibitors (anakinra): The US FDA has approved a recombinant human IL-1 receptor blocker (anakinra) to prevent its use in the treatment of cryopyrin-associated periodic syndromes and rheumatoid arthritis, including multisystem inflammation in newborns [101]. It is effective in treating macrophage activation syndrome and hemophagocytic lymphohistiocytosis [102,103]. Patients with COVID-19 and other disorders, including

macrophage activation syndrome, have elevated endogenous IL-1 levels. State reports have indicated a survival interest in sepsis and a reversal of cytokine storm in patients treated with anakinra [104,105].

Interleukin-6 (IL-6) inhibitors: IL-6 is a pro-inflammatory cytokine produced by various cell types, including lymphocytes, monocytes, and fibroblasts. SARS-CoV infection leads to a dose-dependent production of IL-6 by bronchial epithelial cells [106]. Respiratory failure and systemic inflammation with hypoxia are associated with elevated blood levels of IL-6, D-dimer, C-reactive protein, and ferritin, all of which are related to the critical phase of COVID-19 [107]. Thus, IL-6 was proposed as a potential target for immunotherapy to treat SARS-CoV-2 infection [108].

Kinase inhibitors: The majority of cellular pathways are regulated by kinases, particularly those involved in signal transduction, including tyrosine protein kinase (BTK) and Janus kinase (JAK). Central cellular responses toward exogenous signals in the immune system are also mediated by these enzymes [108]. Thus, excessive host inflammation can be mitigated through the inhibition of certain enzymes. BTK inhibitors (such as acalabrutinib, ibrutinib, and zanubrutinib) are approved by the FDA to treat B-cell malignancies [109]. JAK inhibitors (such as ruxolitinib and tofacitinib) are approved for use in the treatment of ulcerative colitis, polycythemia vera, myelofibrosis, psoriatic arthritis, rheumatoid arthritis, and graft-versus-host disease by the US Food and Drug Administration [110]. Other inhibitors such as kinase can be used for the treatment of COVID-19, because they activate immunity and inflammation (the cellular response to proinflammatory cytokines such as IL-6) and help prevent the phosphorylation of key proteins involved in signal transduction.

Adjunctive therapy

Adjunctive therapies may serve as supplementary alternatives for patients with COVID-19 to treat infection or its complications, as well as to prevent further infection. In addition, antiviral drugs are used to manage COVID-19.

a-Antithrombotic therapy:

SARS-CoV-2 infection is associated with elevated fibrin, fibrin dissolution products, fibrinogen, and D-dimers, thereby heightening the incidence of thromboembolic disease [111,112,113]. Acute respiratory distress syndrome is one of the most common complications of COVID-19, and this syndrome is due to the activation of the coagulation system, which plays a pivotal role [114]. As a result, respiratory dysfunction occurs gradually with heart failure, resulting in the development of microthrombi, ferritin, and platelets in blood vessels. The WHO recommends the administration of antithrombotic therapy, specifically low-molecular-weight heparin (such as enoxaparin) in hospitalized patients for COVID-19 in the absence of contraindications. For those who have contraindications, pneumatic devices (Intermittent pressure devices) are recommended.

b. Vitamins and minerals:

Some physicians advocate mineral supplements and vitamins as the optimal treatment for viral respiratory infections. Many ongoing studies are evaluating the use of vitamins and minerals in conjunction with therapy and protection against SARS-CoV-2 infection. Recent studies have shown that some micronutrients and herbs may be used to reduce risk, decrease mortality, and/or treat COVID-19. The authors conducted an online search using the terms MERS, SARS, and respiratory viruses to achieve this goal. The results of the systematic study showed that several nutrients including vitamins D, A, E, C, and B complex, as well as zinc, selenium, iron, and herbs (such as garlic, black seed, and licorice), can be used as urgent supportive agents that can improve the immune system and help alleviate COVID-19 [115].

Vitamin (C): L-Ascorbic acid, a water-soluble compound, has displayed promising outcomes in the treatment of viral infections [116]. It functions as an antioxidant and a free radical scavenger, with anti-inflammatory features, influencing cellular immunity and vascular integrity and catalyzing the production of endogenous catecholamines [117, 118].

Vitamin (D): This is important for bone and mineral metabolism. Vitamin D can modulate adaptive and innate immune responses because the vitamin D receptors, which are expressed in immune cells such as T cells, B cells, and antigen-presenting cells, enable these cells to synthesize the active metabolite of vitamin D [119]. Vitamin D deficiency is common among older patients and those who are obese and hypertensive; these

characteristics are associated with poor outcomes for patients with COVID-19 [120]. The levels of T-regulatory cell activity in patients with autoimmune diseases and healthy individuals are elevated with vitamin D supplementation [121]. It is also linked to the mitigation of acute respiratory infection risk [122]. Kidney calcification and hypercalcemia may result from high levels of vitamin D [123].

Zinc: Zinc plays a critical role in the immune system, regulating leukocyte and lymphocyte proliferation, differentiation, maturation, and function [124], as well as modulating inflammatory responses [125]. Given the high ratio of Zn deficiency worldwide (17%), its influence on the health of the population is a major issue [126]. In addition, exposure to the risk of infection due to zinc deficiency and its harmful effects on certain populations, especially premature babies and the elderly, is noteworthy [127]. Changes in zinc status have a significant effect on immune response, contributing to increased vulnerability to inflammatory and infectious diseases, including ADIS, measles, malaria, tuberculosis, and pneumonia [128]. Zn^{2+} cations have been shown to inhibit SARS-coronavirus RNA polymerase activity, particularly during the integration of the Zn ionophore, by reducing its replication [129]. Thus, Zn(II) may be considered an antiviral agent in COVID-19 therapy. Clinical experiments have demonstrated that chloroquine exhibits antiviral efficacy activity as a treatment for COVID-19 [130]. Previous findings indicated that chloroquine is a zinc ionophore that increases Zn(II) flow into the cell [131]. Similarly, growing intracellular Zn^{2+} condensation through chloroquine may facilitate its antiviral effects against SARS-CoV-2. Thus, zinc supplementation without chloroquine may yield similar beneficial effects without the adverse side effects associated with chloroquine therapy [132].

Mutated coronaviruses:

Mutated coronaviruses refer to further mutations that researchers continue to investigate today. Numerous researchers remain largely uninformed about the variables of the coronavirus, including the extent of their distribution, rates of transmission, and the effect of the resulting mutations on vaccines and diagnostic tests. Viruses can spontaneously mutate and replicate within host cells, where the majority possess genetic material in the form of RNA or DNA. Mutations in viruses arise from their genetic molecules, varying by virus type. Typically, RNA viruses exhibit a higher mutation rate compared with DNA viruses. Notably, two types of RNA viruses with high mutation rates are HIV and influenza. SARS-CoV-2 is an RNA virus, but it demonstrates a slower mutate rate compared with other viruses. Another RNA is nuclear. Viruses use an enzyme called polymerase to replicate their genetic material. However, this polymerase is imperfect, resulting in errors that lead to mutation, which may be detrimental or helpful to the virus. Harmful mutations affect the ability of the virus to transmit infection and replicate inside the host cell. These viruses cannot survive in the presence of this mutation due to their impaired functionality. This mutation has the advantage of enhancing the virus's affinity for host cell binding or facilitating its escape from the immune system. Recently, similar characteristics were identified in New York (California Trusted source) [133], and a large proportion of these variables remain unknown. Nonetheless, scientists continue to discover and characterize these variables for the new coronaviruses. The following types are some of these variables:

B.1.1.7 variant: The Alpha variant, known as the SARS-CoV-2-Alpha-variant, was identified in the United Kingdom in the fall of 2020 and then spread to become the most prevalent strain there. This strain has also been found in 80 other countries, including the United States, prompting public health officials to express concerns that B.1.1.7 may become the most rapidly disseminating strain in the United States. This variant is characterized by multiple mutations that affect the spike protein, which is found on the virus' surface that interacts with host cells and affects the body. Public health officials in the United Kingdom have found that this variant is transmitted rapidly among people, with a transmission rate up to 50% higher than the original virus. These mutations enhance the spike protein's adhesion to host cells, and this finding was corroborated by experiments and studies. Research indicates that B.1.1.7 samples are associated with a high percentage of viral load, so an increase in this viral load can facilitate rapid transmission of infection among infected individuals, resulting in a rise in the number of disease

cases and hospitalizations. The number of deaths necessitates considerable efforts from health systems [134].

B.1.351variant: The Beta variant is classified under the lineage SARS-CoV-2 B.1.351. Its presence was first confirmed in South Africa in early October 2020, thereafter identified in 41 countries, including the United States, which exhibited variations. The B.1.351 variant has some spike protein mutations found in the previous B.1.1.7 mutant identified in the United Kingdom, along with other mutations. To date, there is no evidence indicating that the B.1.351 variant causes severe disease associated with coronaviruses. However, they found that mutations of this variant can affect immunity or antibody responses. In 2021, a study demonstrated that this B.1.351 variant may escape the effect of isolated antibodies for individuals with a previous infection with COVID-19 [135]. Antibodies are immunological proteins that can bind and block the effects of other viruses. Or neutralize its action, so it is produced as a natural response to infection or as an important and effective vaccine for this reason because B.1.351 may avoid the effect of antibodies, so people infected with the new Coronavirus can be infected with this new variant despite their current immunity, and this means that the effect of vaccines is less effective in the case of infection with this mutagen, another reliable study in Zambia proved that 22 out of 23 samples collected within a week, one sample of B.1.351 was not detected out of 245 previously collected samples, and at the same time, this discovery occurred an important increase at states. Incidence from COVID-19 in Zambia.

P.1 variant: This variant is called p.1 / Gamma, and it is also known as SARS-Co-V-2 (P.1Gamma). This mutant was discovered at the beginning of January 2021 among travelers from Brazil. This virus was also found in the USA at the end of January 2021. In general, information about this mutant is insufficient compared with the previous mutant, as the P.1 mutant contains 17 rare mutations, including some basic mutations in the key spike protein, which was investigated in South Africa and the United Kingdom with the emergence of several mutations. The transmissibility and spread of P.1 may have been pronounced in the samples collected during January 2021, coinciding with a surge in cases of COV-19 in Manaus, Brazil [136], where the variant was absent in prior samples and shared mutations with the B.1.351 variant. Therefore, the variant affects the effectiveness of the vaccine and immunity, as proven by documented evidence, including a statistical study of the COVID-19 wave in Manaus involving blood donors. About 76% of humans were infected with the new coronavirus by October 2020, leading to the conclusion that there is an increased likelihood of reinfection with P.1 among these individuals.

SARS-CoV-2 (Delta) variant: This variant was discovered in the United States, having first been confirmed in India in December 2020. This mutated strain rapidly proliferated in India and spread to Britain before reaching the United States at an accelerated pace. It has become the predominant variant of SARSCo-V-2, accounting for 99% of COVID-19 cases and demonstrating a notable rate of recovery in some states. Research has demonstrated that the Delta virus causes infections at more than double the rate of previous strains. Moreover, unvaccinated individuals hospitalized for COVID-19 face a heightened risk of infection. Thus, the highest prevalence rates of this variant are observed in areas with low vaccination coverage [137].

Delta plus variant: This variant derives its name from the previous Delta variant, so it was called Delta Plus, indicating the presence of a new mutation in the spike protein used by this virus to infiltrate human cells. This newly modified strain has been identified in relatively low quantities [138]. This variant has a large number of mutations B1.1.529. According to South African scientists who first discovered the Beta variant, this new strain emerged as a result of a global surge in coronavirus infections since its first discovery in South Africa and Botswana, prompting the WHO to express concern regarding this variant.

Omicron variant: This variant is characterized by a large number of mutations, between 26 and 32, raising concerns about its ability to evade vaccination efficacy, particularly against the BA.5 and BA.4 variants, as well as its rapid transmissibility. The spread of the spike protein invades the body's cells [139].

Corona virus mutations and vaccines

With the continued rapid spread of novel coronavirus variants and the emergence of new vaccines designed to mitigate transmission through vaccination, we will highlight four important vaccines that have

proven effective in treating individuals infected with COVID-19.

Pfizer-BioNTech BNT162b2 Vaccine: Developed by Pfizer, this vaccine utilized several techniques in its production, demonstrating a recovery rate of 90% for the mRNA vaccine. This vaccine is an exceptional case because it was administered to individuals between the ages of 5 and 16 years old (140, 141).

Sino pharm vaccine (Chinese vaccine): This traditional vaccine was produced using established traditional technology, as it is manufactured from virus particles that have been cultivated and are incapable of causing disease [142]. This vaccine has demonstrated efficacy for individuals aged 18–60, although it is contraindicated for those above 60 years old [143].

Oxford-AstraZeneca vaccine: Developed at the University of Oxford, this vaccine, a replication-deficient chimpanzee adenoviral vector, contains a structural surface glycoprotein antigen chAdox of COVID-19. It has shown cure rates of up to 70.4% for COVID-19 cases and exhibited enhanced protection of 73% in individuals with one underlying medical condition. The vaccine has also shown no difference in immune response between older and younger healthy individuals [144,145].

Moderna vaccine: This vaccine received emergency use authorization on December 18, 2020 (EUA), and it was distributed in the United States to infected people aged 18 years or older [146]. An mRNA molecule found in the Moderna vaccine provides instructions on how to make a protein from SARS-CoV-2. COVID-19 cannot induce the virus, as it does not contain it [147]. Although the USA FDA has authorized several effective and safe vaccines for emergency use, even less effective vaccines remain beneficial in preventing COVID-19 infection. Forecasting future events in the forthcoming years is impossible. The question is who will win the race, and whether we will find effective and safe vaccines for the final prevention of infection and their risk. The virus may cease to exist permanently without the need for ongoing vaccination. By contrast, variants or mutated strains of the virus that are more lethal, more contagious, and more pervasive than the original strain may emerge, thereby diminishing the efficacy of the vaccine. The future could introduce new events, variables, and circumstances that may influence the mutated virus and the vaccines used for immunization.

Conclusion

The review on the diagnosis and treatment of COVID-19 emphasized the importance of accurate diagnosis through a combination of viral detection tests, antibody detection tests, and imaging findings. Treatment focuses on supportive care, symptom relief, antiviral therapy, immunotherapy, and personalized approaches based on disease severity and patient characteristics. This review also discussed the historical context and genetic diversity of SARS-CoV-2 treatment methods, revealing the absence of a definite cure. The researchers agreed on the importance of implementing appropriate healthcare interventions based on the severity of viral infection and the incidence rate. This study concluded that the results of the systematic analysis showed that several nutrients including vitamins D, A, E, C, and B complex; zinc; selenium; iron; and herbs such as garlic, black seed, and licorice can be used as urgent supportive agents that can improve the immune system and help alleviate COVID-19. The mutated coronaviruses, such as the Delta and Omicron variants, were highlighted, along with strategies for managing each variant. This review emphasized the need for continuous research, vigilance, and adaptability to evolving viral strains, particularly regarding the use of four WHO-approved vaccines for different age groups, which helped limit the spread of the virus despite the emergence of new variants amid scientific progress in research and studies in this field.

Acknowledgments

I would like to extend my profound gratitude to my esteemed professor colleagues who contributed to the presentation and evaluation of this comprehensive review through the proposed scientific terminology and required scientific study. I would also like to thank all Iraqi universities and international research centers, including the Children's Hospital in Baghdad, for the resources they provided to obtain the appropriate scientific references.

Conflict of Interest

Author/s should declare any relevant conflict of interest.

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P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2025,(19), (01):58 – 78

فيروس كورونا المستجد، تاريخه، تشخيصه، التنوع الجيني والعلاج: مراجعة شاملة

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الخلاصة:

تستعرض هذه المقالة بشكل شامل تاريخ ،تشخيص، تنوع الجينات وعلاج فيروس كورونا المستجد. وتوضح بالتفصيل ظهور فيروسات كورونا على مدار الخمسين عامًا الماضية، بما في ذلك فيروس كورونا المستجد من عام 2019، والطفرات اللاحقة، مع معلومات محدثة. أوضحت هذه المراجعة تكوين وتسمية فيروسات كورونا، وغزوها للخلايا من خلال طفرات الجليكوبروتين التي ترتبط بمستقبلات **ACE-2**، وعملية دخول الخلايا عن طريق البلعمة الذاتية. وتناقش طرق تشخيص كوفيد-19، بما في ذلك تضخيم الأحماض النووية، وعلم الأمصال، والتصوير مثل الأشعة السينية للصدر واختبارات التصوير المقطعي المحوسب. كما تم تحديد طرق علاج كوفيد-19، مع التركيز على الرعاية الصحية، والأدوية المضادة للفيروسات مثل ريمديسيفير، والعلاج المناعي باستخدام بلازما النقاهة، والعلاجات المساعدة مثل مضادات التخثر والفيتامينات. كما يسلط النص الضوء على فيروسات كورونا المتحولة مثل متغير دلتا ومتغير أوميكرون، ويستكشف تأثيرها على استجابة اللقاح. تتناول هذه المراجعة خصائص وتأثير المتحورات مثل **B.1.1.7** و **B.1.35 1** و **P.1** و **Delta** و **Delta plus** و **Omicron**، مع مناقشة طفراتها التي تؤثر على انتقال الفيروس وفعالية اللقاحات مع عرض مختصر لأربعة لقاحات معتمدة من قبل منظمة الصحة الدولية ومدى تأثيرها ضد المتحورات الجديدة المحتملة.

الكلمات المفتاحية: كوفيد-19، التشخيص، العلاجات، الفيروسات المتحولة، ظهور فيروسات كورونا.