Lessons from SARS-CoV-2 and its variants (Review)

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Received April 17, 2022; Accepted June 1, 2022

DOI: 10.3892/mmr.2022.12779

Abstract. COVID-19 has swept through mainland China by human-to-human transmission. The rapid spread of SARS-CoV-2 and its variants, including the currently prevalent Omicron strain, pose a serious threat worldwide. The present review summarizes epidemiological investigation and etiological analysis of genomic, epidemiological, and pathological characteristics of the original strain and its variants, as well as progress in diagnosis and treatment. Prevention and control measures used during the current Omicron pandemic are discussed to provide further knowledge of SARS-CoV-2.

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Key words: SARS-CoV-2, COVID-19, variant, diagnosis, treatment

1. Introduction

COVID-19, caused by novel coronavirus SARS-CoV-2, has posed a serious threat to human health and public safety globally with rapid transmission and serious pathogenicity (1). Novel variants of the original virus are emerging on a frequent basis. Omicron strain has rapid speed of transmission and has replaced Delta strain as the most prevalent currently, causing large scale global infection, it was first discovered in Johannesburg, South Africa, then identified in Belgium, Israel, Hong Kong and European countries (2). The Omicron cases in South Africa peaked at 40,000 per day (Dec 2021), while UK had >100,000 cases per day (Dec 2021), with Omicron accounting for 90% of all patients with COVID-19 in London (3,4). Omicron has been identified in >100 countries and has caused >1 million daily cases up to 3rd June, 2022 (2).

SARS-CoV-2, a single-stranded RNA β-coronavirus genus, is enveloped by membrane with polymorphic shape, commonly round or oval (5). Glycoproteins on the membrane surface include spike (S) protein, which serves as a receptor-binding and antigenic sites that trigger cytolysis by inducing antigenic response (6); small envelope (E) glycoprotein, which mediates binding to the envelope; membrane (M) glycoprotein, which is responsible for nutrient transmembrane transport, budding release of virus and formation of virus envelope and nucleocapsid (N) protein, which can be used as a diagnostic antigen and encapsulates the viral genome (7). As heavily glycosylated S trimers, S proteins bind to the human angiotensin converting enzyme 2 receptor (ACE2) and mediate viral entry into target human cells, making S protein the most important in the pathogenesis of infection (8). SARS-CoV-2 infects humans by binding to ACE2, which is the same host receptor for SARS-CoV. SARS-CoV-2 binds ACE2 of respiratory epithelial cells before multiplying, passing through the airways and finally entering alveolar epithelial cells (9). Massive viral duplication in the lung triggers the immune response, which causes aggregation and accumulation of inflammatory cells, resulting in typical symptoms of viral pneumonia (10). Acute pulmonary infection can cause complications, the most severe of which are acute respiratory distress syndrome (ARDS) and respiratory failure, which have become the leading cause of death during the epidemic (11,12). A cohort study of 459

intensive care units from 50 countries and 5 continents found that the mortality rate is 26.0-61.5% for patients with ARDS who received critical care and 65.7-94.0% for patients who received mechanical ventilation (12).

Similar to other viruses, the novel coronavirus genome exhibits variations that may alter its biological features. Changes in the affinity of S protein and ACE-2 may affect viral invasion of cells, replication and transmission, production of antibodies during recovery or following vaccination, the neutralization activity of antibody may be impaired (13). Delta variant (B.1.617.2) exhibits 23 mutations compared with the original strain, 12 of which are in the novel S protein (14). The increased number of mutated S proteins make immune recognition and antibodies attachment more difficult, leading to a higher infection rate in human cells (15). The newly reported Omicron strain exhibits a considerable number of mutations in S protein as well. Among 50 mutations, 23 of them are in the S protein, preventing antibodies from attaching to S protein, resulting in increased transmissibility and infectivity (16).

2. Epidemiological features

SARS-CoV-2 appears to be particularly infectious in crowded places with poor ventilation and the chance of infection following exposure to SARS-CoV-2 is similar between different age groups (17), while people appear to develop a degree of immunity following vaccination or infection.

Compared with the original strain, variants exhibit similar epidemiological features. Although there is no conclusive evidence that Delta variant causes distinct symptoms from Alpha, patients infected by Delta variant exhibit more rapid onset and higher viral expression in the respiratory tract (18). It is hypothesized that the infectiousness of Delta variant is double that of the original strain, indicating a higher potential infection and death rate (19). Omicron variant is notably more contagious compared with Delta as a result of its mutations on the S protein receptor-binding domain (RBD) (20). Patients infected with Omicron variant often present with mild symptoms and severe symptoms are rare (21). In terms of age, it has a greater impact on young and middle-aged people than previous variants (22). Omicron also exhibits greater ability to escape from antibodies, which can lead to more cases of reinfection and infection following vaccination (20).

During outbreaks, however, clinical features differ between age groups. According to a study (23), the incidence of pre-existing comorbidities such as hypertension, diabetes and cardiovascular disorder is higher among the elderly (age, >60 years), who may have more underlying disease and be in poorer physical condition compared with young and middle-aged groups. Regarding pulmonary infection and comorbidities, elderly patients have a higher risk of severe respiratory disease requiring intensive care (24), while younger patients may only exhibit moderate pneumonia, asymptomatic infection or be less likely to develop COVID-19 (23). Additionally, studies have indicated that immunocompromised hosts, such as patients with HIV or active cancer or receiving high-dose steroid therapy, may be more likely to develop complications following infection with SARS-CoV-2 (25,26).

Infected people are the primary source of infection, as well as asymptomatic patients and patients in latent period (27). It is hypothesized that transmission via aerosols is the primary route from infected patients to non-infected people (28). Patients in latent period without symptoms also discharge virus particles into the environment at similar levels to symptomatic patients, which poses a threat to public safety (29).

Droplets are the primary infective agents of SARS-CoV-2. When a patient breathes, coughs or sneezes, respiratory droplets with high viral load are expelled from the mouth and nose (30). Infected people produce an aerosol form of SARS-CoV-2 as particles (diameter, <5 μm) suspended in gas (31). However, the likelihood of infection depends on the distance between the source and the susceptible person (32). Short-distance airborne transmission, including via droplet and aerosol, which is also known as 'direct contact', may serve as the principal pathway of virus dissemination (33). On the other hand, 'indirect contact' occurs when pathogens exhaled by carriers of SARS-CoV-2 contaminate objects and infect susceptible individuals exposed to them (34).

Epidemiological analysis and pathogenesis indicate the respiratory tract is the primary route of infection (35). $ACE2^+$ cells in the respiratory tract are viral receptors and may be responsible to human-to-human transmission (36). Droplets and aerosol carrying the virus enter the respiratory track of susceptible person, typically in the form of saliva, sputum and nasal secretion, and begin to multiply by binding ACE2 (Fig. 1) (37). Other routes of transmission such as fecal-oral, mother-to-child and body fluid transmission are controversial and lack direct, real-word evidence. Nosocomial infection is a key route of virus transmission. Samples of item surfaces and air from confirmed patient wards were tested positive, implying that SARS-CoV-2 can spread in examination rooms and wards (38), which indicates the necessity of guarding against infection during clinical activity requiring open mouth and contact with body fluids, such as endoscopy, dental treatment and pulmonary function test (39).

3. Clinical and pathological manifestation

Based on an epidemiological survey, the incubation period for COVID-19 is 1-14 days, with the majority of cases lasting 3-7 days (40). Fever, dry cough and exhaustion are reported as the three most prevalent symptoms, while certain patients exhibit expectoration, nasal obstruction, runny nose, sore throat, emaciation, hemoptysis, headache, chest pain, chills, myalgia, gastrointestinal responses and olfactory and taste disorder (41,42). Vaccinated people or those infected with Omicron generally present with asymptomatic infection or mild symptoms, while symptomatic patients primarily manifest with upper respiratory infection (43). Dyspnea and hypoxemia are the main manifestations of severely ill patients and typically develop within one week of symptomatic presentation (30). Severely ill patients rapidly develop ARDS, septic shock, coagulopathy, refractory metabolic acidosis and multiple organ failure. Certain patients develop central nervous symptom disorder and acral ischemic necrosis of the extremities (1). Severely or critically ill patients may present with moderate to low fever, while mild patients present with slight weariness, odor and taste disturbance, as well as low fever, but

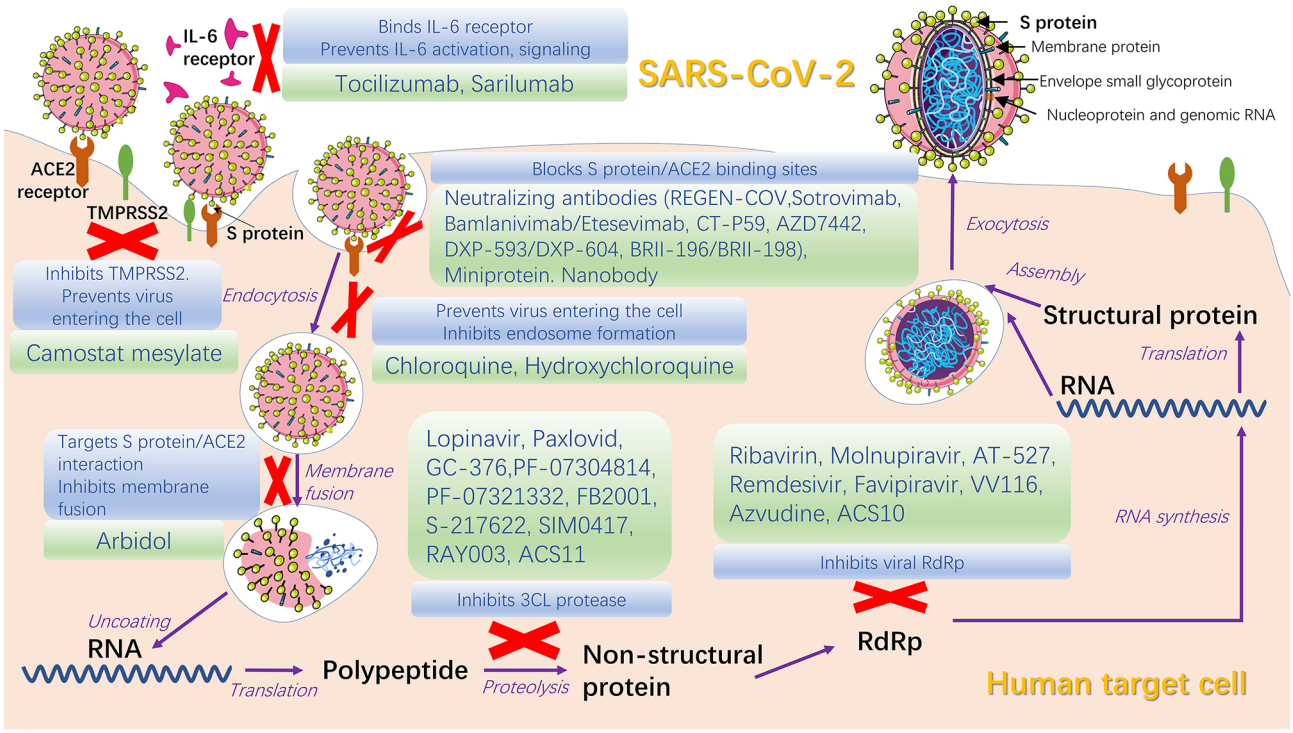

Figure 1. SARS-CoV-2 structure, pathogenesis of SARS-CoV-2 infection, and molecular target of different therapies against COVID-19. SARS-CoV-2 uses its S proteins to bind to ACE2 receptors to enter human cells. Following endocytosis and membrane fusion, uncoated RNA is translated to polypeptide, then non-structural proteins such as RdRp. The viral RNA is synthesized and structural proteins are translated; these and assemble into new viruses before released into human cells. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S, spike; ACE2, angiotensin-converting enzyme 2; RdRp, RNA-dependent RNA polymerase; TMPRSS2, transmembrane protease, serine 2; 3CL protein, 3-chymotrypsin-like protease.

no visible signs or symptoms of pneumonia (44). According to a study in China, mild cases form the majority of total cases, while severe cases requiring intensive care and critical cases with life-threatening emergency complications represented <20% of the study population (45). As aforementioned, the risk level of COVID-19 varies by age. In addition, age and male are risk factors for cardiovascular disease, therefore, elderly men infected by SARS-CoV-2 may have a higher risk of developing severe cases with respiratory and circulatory failure, while the young and middle-aged people may be able to recover in two weeks (44).

In the early phase of COVID-19, peripheral blood displays lymphopenia and decreased or normal leukocyte count, while certain patients present with high levels of aspartate aminotransferase, lactate dehydrogenase, myoglobin, creatine kinase, troponin and ferritin. In terms of inflammatory indicators, C-reactive protein and erythrocyte sedimentation are increased in the majority of patients (9). Increased expression of D-dimer and decreased peripheral lymphocyte levels may present in severe cases (46). Hypercytokinemia, characterized by high expression of cytokines in plasma, is common in severely and critically ill patients, potentially resulting in death within 16 days of disease onset (47).

Computerized tomography (CT) scanning of the patient chest commonly reveals bilateral patchy shadow or ground-glass opacity with subpleural, centrilobular and diffused distribution (48). The tiny shadows rapidly expand into a scattered distribution as the disease progresses. Organizing pneumonia and fibrosis are primarily observed in the later stages of COVID-19 without pleural effusion (49).

Histological examination shows bilateral diffuse alveolar injury with mucinous exudation of cellular fibers, desquamation of pneumocytes and fibrin deposits and hyaline membrane formation, which indicate the occurrence of ARDS (50). In the course of COVID-19, inflammatory infiltration of mononuclear cells, primarily lymphocytes, occurs in alveoli, which indicates that directional aggregation of lymphocytes may lead to peripheral lymphopenia. Alveolar cells exhibit large nuclei, double cytoplasmic granules and obvious nucleoli, indicating cytotoxic alteration, which is also observed in other organs, such as spleen, hilar lymph node, bone marrow, heart and blood vessels, liver, gallbladder, kidney, adrenal gland, alimentary epithelial cells, brain and testicles (51).

Nucleic acid detection is primarily used for etiological examination. By serological examination, specific IgM induced by SARS-CoV-2 infection can be detected; positive results of IgG antibody may be seen within the first week of onset (52).

A cohort study of patients recovering from COVID-19 reported symptoms including weariness, muscle discomfort, sleeping difficulty and psychological problems such as anxiety or depression 6 months after the onset of COVID-19. Severely ill patients exhibited more obvious symptoms following recovery; in addition to impaired pulmonary diffusion function and damaged (as revealed by chest imaging), cardiovascular, nervous, digestive, urinary and immune symptoms were observed (53,54). Therefore, recovery following COVID-19 still requires long-term epidemiological investigation.

4. Diagnosis

During the Omicron epidemic, RT-qPCR nucleic acid detection was used as the gold standard for diagnosis of COVID-19 (55). For unvaccinated patients, detection of specific antibodies such as IgM and IgG are used as a diagnostic reference. However, for those who have been vaccinated or have a history of previous infection, these antibodies may not have diagnostic value (56).

Omicron appears to cause more asymptomatic cases and patients with mild symptoms or in the incubation period can lead to wide and undetected viral spread (57). Therefore, early identification and close monitoring of suspected cases are key for public protection against Omicron. Based on current studies (55,57), symptoms caused by SARS-CoV-2 variants vary between infected individuals, which yields limitations in common detection methods. Therefore, absence of respiratory symptoms and pulmonary inflammation or negative PCR test do not mean the patient is non-infectious, indicating that early recognition is critical during clinical tests (58). Diagnostic techniques must be updated to be more sensitive and adaptable to emergence of novel variants.

RT-qPCR is used for rapid detection of SARS-CoV-2. Compared with next-generation gene sequencing (NGS), it is faster and cheaper, provides clear results and has a larger sample capacity (59). Lower respiratory tract samples exhibit higher viral load compared with samples from other sources, with oral and nasopharyngeal swabs being most convenient and commonly used (60). Negative RT-qPCR results from respiratory samples have been obtained while positive results were obtained from intestinal canal and peripheral blood (61), indicating that isolation of live viruses is key to assess virus reproduction (62). The outcome of RT-qPCR nucleic acid detection tends to be inadequate due to complicating factors (57). False negative results can be due to virus mutations that make primers and probes difficult to recognize, low viral load in samples caused by viral mutations or non-standard sampling, different detection reagents and poor quality control (63,64). Therefore, screening hospital patients via RT-qPCR may be insufficient and multiple approaches are needed for confirmation of the novel coronavirus. Specific primers targeting key mutations in S protein rapidly recognize variants of concern that may differ from previous Omicron mutations (65). Metagenomic NGS should also be used to analyze nucleic acid, especially for patients who may be infected with a SARS-CoV-19 variant (66). Loop-mediated isothermal amplification, which is highly specific for mutations, detection with 6-8 specific primer sequences, may be substitute for a RT-qPCR diagnosis (67). Contact tracing is required to avoid the omission of potential transmitters and help to cut off the transmission route.

Serology can be used for diagnosis along with RT-qPCR. Antibody-based techniques are not recommended for early detection owing to the long period for inducing antibody responses, while antigen-based immunoassays such as ELISA assess immune response and disease progression by detecting N or S protein on antibodies (68). However, serology cannot exclude the effects of cross-reactivity caused by factors such as muramidase, rheumatoid factors and heterophile antibodies (69). The intensity and duration of immune responses may differ between individuals and disease stage and serological tests exhibit varying sensitivity and specificity, creating obstacles to their application, while biosensor technologies may improve the specificity and sensitivity of diagnosis (70).

Chest X-ray or CT imaging are also used as diagnostic techniques for the novel coronavirus (71). Bilateral ground-glass opacity is indicative of SARS-CoV-2. The sensitivity of chest CT has been proven as it accurately diagnoses infection in the presence of negative RT-qPCR results (72). Therefore, chest CT combined with repeated RT-qPCR may be a reliable technique for suspected cases with negative initial RT-qPCR detection (73). However, improper technique and atypical manifestation can result in false negatives (71).

Recently, artificial intelligence (AI) as an emerging technology for interpreting chest imaging and quick diagnosis of COVID-19 has been widely discussed (74-76). AI applications are used in imaging platforms, region segmentation for lung infection, clinical assessment and auxiliary diagnosis based on meta-analysis (74). Based on its operational principles of interpreting chest imaging and quick diagnosis (77), it may also contribute to clinical and basic research associated with SARS-CoV-2, in addition to assisting diagnosis in clinical practice. Accurately distinguishing COVID-19 from other respiratory disease improves the efficiency of diagnoses and simplifies workflow, which primarily depends on manual work of radiologists, providing more accurate results and maintaining safety of medical staff during examination (75). At this stage, AI diagnosis still needs to improve image acquisition and expand sample capacity, which is the foundation of segmentation and diagnosis (76). For physicians, AI results of chest imaging must be considered in light of clinical manifestation and laboratory examination (78).

5. Treatment

Currently, numerous specific targeted medicines have passed phase III clinical trials and proven to have therapeutic efficacy against COVID-19, despite preliminary or controversial results of clinical trials. Existing antiviral drugs and their combination are recommended, while extensive tests are needed to demonstrate the effectiveness and pharmacokinetic and safety profiles of specific targeted drugs before widespread use as a therapy for COVID-19 (Table I) (79).

Antiviral medicines for SARS-CoV-2 can be divided into two groups based on the molecular mechanism: Drugs targeting viral protein or RNA and drugs targeting host protein or biological processes that allow viral entry into cells (80). Antiviral therapies should be used in the early stage of disease, especially for patients with higher risk of developing severe illness, as early intervention is more effective compared with treatment in severe cases (81).

Interferon, which confers congenital immunity to viruses, induce the expression of antiviral proteins (AVPs) such as 2'-5'A synthase and protein kinase to impede viral replication (82). Interferon-α has been demonstrated by studies to be effective against SARS-CoV and may be more sensitive against SARS-CoV-2 (83). COVID-19 guidelines in China recommend interferon-α as an antiviral drug (84). Interferon-β has proven useful in certain trials (85,86) but further studies are needed to evaluate its effectiveness in high-risk cases.

Table I. Antiviral and antibody-based therapy for COVID-19.

A, Antiviral therapy

Name	Company	Indication	Mechanism of action	Effectiveness	(Refs.)
Interferon-α, Interferon-β	Multiple	Viral infection and certain types of malignant tumor	Protects lower airway	No obvious therapeutic effect on hospitalized patients with COVID-19	(191)
Interferon-γ	Eiger Biopharmaceuticals	Early phase of mild COVID-19	Protects upper and lower airway continuously, inhibits cytokine storm	Risk reduction of hospitalizations or ER visits, 50% (trial no. NCT04967430)[a]	
Lopinavir	Multiple	HIV-1 infection	Inhibits HIV-1 3CLpro	Lopinavir + ritonavir has no obvious therapeutic effect on hospitalized patients with COVID-19 (trial no.ChiCTR2000029308)[a]	(89)
Ritonavir	Multiple	HIV-1 and HIV-2 infection	Inhibits CYP3A4 activity, decreases metabolism of antiviral agents		
GC-376	N/A	Feline infectious peritonitis	Inhibits SARS-CoV-2 3CLpro	Potential	(192)
PF-07304814, PF-07321332	Pfizer	COVID-19	Inhibits SARA-COV-2 3CLpro	Potential	(193)
Paxlovid (nirmaterevir + ritonavir)	Pfizer .	Patients with mild-to-moderate COVID-19 (adults and children aged >12 years) with high risk of transforming into severe cases	Nirmatrevir inhibits SARS-COV-2 3CLpro, ritonavir serves as an adjuvant	Risk reduction of hospitalization or ER visit, 89% (trial no. NCT04960202)[a]	(194)
Umifenovir (Arbidol)	BHBT	Influenza	Targets interaction between influenza virus S protein and ACE2 of host cells, induces interferon	Potential (trial no. IRCT20180725040596N2)[a]	(195)
GeLactoferrin	N/A		Targets HSPGs, prevents virus attaching to cells.	Potential	(196)
Camostat mesylate	N/A	Acute symptoms of chronic pancreatitis	Inhibits TMPRSS2 and protease, trypsin and matriptase activity	Potential	(197)
Remdesivir (GS-5734)	Gilead Sciences, Inc.	Ebola and Marburg virus, patients with mild-to-moderate COVID-19 (adults and young children aged >28 days and weighing ≥3 kg)	Inhibits expression of viral RNA polymerase	Requires verification. (trial no. NCT04257656.)[a]	(198)
Favilavir/ Favipiravir (T-705)	FUJIFILM Wako Pure Chemical Corporation	Influenza, RNA virus infection	Inhibits expression of viral RNA polymerase	Requires verification	(199)

Table I. Continued.

A, Antiviral therapy

Name	Company	Indication	Mechanism of action	Effectiveness	(Refs.)
Molnupiravir (MK-4482/ EIDD-2801)	MSD, Ridgeback Biotherapeutics LP	Patients with mild-to-moderate COVID-19 (adults)	Inhibits expression of viral RNA polymerase	Risk reduction of hospitalization or death, 50%, (trial no. NCT04575597)[a]	(108)
Bemnifosbuvir (AT-527)	Roche, Atea Pharmaceuticals	Patients with mild-to-moderate COVID-19 not requiring hospitalization	Inhibits expression of viral RNA polymerase	Requires verification. Did not meet primary clinical endpoint (trial no. NCT04709835)	(109)
Merimepodib (VX-497)	N/A	RNA virus infection	Inhibits IMPDH, suppresses replication of RNA virus	Potential	(200)
Plitidepsin	PharmaMar	Multiple myeloma	Inhibits eEF1A	Potential	(110)
Fluvoxamine	Multiple	Depression, mild COVID-19	Inhibits selective serotonin reuptake	Requires verification (trial no. NCT04342663)[a]	(114)
Chloroquine, hydroxychloioquine	N/A	Malaria and rheumatoid arthritis	Inhibit TLRs	Potential but with obvious side effects	(96)

B, Antibody-based therapy

Name	Company	Indication	Mechanism of action	Effectiveness	(Refs.)
Convalescent plasma	N/A	Patients with COVID-19 with high risk factors, rapid progression or severe or critical COVID-19	Purified neutralizing antibody agains t SARS-COV-2 obtained from recovered COVID-19 patients	Potential but controversial	(201)
Polyclonal antibody	N/A	Transplantation reaction, autoimmune disease	Immunizing animals with antigen containing multiple epitopes stimulates multiple B cell clones to produce antibodies against multiple epitopes	Potential	(202)
Miniprotein	N/A		Artificially designed, high affinity binding to RBD of SARS-CoV-2 S protein	Potential	(203)
Nanobody	N/A		Alpaca-derived antibodies, bind to RBD of SARS-CoV-2 S protein, prevent ACE2 binding	Potential	(204)
Tocilizumab (Actemra)	Roche	Rheumatoid arthritis, severe or critically	Monoclonal antibody, binds to non-signaling	Effective but controversial	(205)

Table I. Continued.

B, Antibody-based therapy

Name	Company	Indication	Mechanism of action	Effectiveness	(Refs.)
		ill patients with COVID-19	site of IL-6 (CD126)	(trial no. NCT04356937)[a]	
Sarilumab (Kevazra)	Sanofi S.A., Regeneron Pharmaceuticals, Inc.	Rheumatoid arthritis, severe or critically ill patients with COVID-19	Monoclonal antibody, targets α subunit of IL-6 receptor complex	Effective but controversial	(132)
Sotrovimab (VIR-7831)	GlaxoSmithKline, Vir Biotechnology, Inc.	Patients with mild-to-moderate COVID-19 (age, >12 years)	Monoclonal antibody, binds to highly conserved epitope of SARS-CoV-2 S protein	Potential but controversial (trial no. NCT04545060)[a]	(206)
Bevacizumab (Avastin)	Roche	Metastatic cancer, severe or critically ill patients with COVID-19	Monoclonal antibody, inhibits VEGF to suppress growth of new blood vessels	Potential	(133)
Bamlanivimab (LY-CoV555) + Etesevimab (LY-CoV016/ JS016)	Eli Lilly and Company, Top Alliance Biosciences	Patients with mild-to-moderate COVID-19 (age, >12 years) with high risk of severe illness or hospitalization	Monoclonal antibody, binds to RBD of SARS-CoV-2 S protein	Risk reduction of hospitalization or death, 70% (trial no. NCT04427501)[a]	(207)
Regdanvimab (CT-P59)	Celltrion	Patients with mild-to-moderate COVID-19	Monoclonal antibody, binds to RBD of SARS-CoV-2 S protein	Potential (trial no. NCT04525079, NCT04593641)[a]	(208)
AZD7442	AstraZeneca plc	Patients with mild-to-moderate COVID-19	AZD1061 + AZD8895 monoclonal antibodies, binds two sites of SARS-CoV-2 S protein	Risk reduction of symptomatic COVID-19, 77% (trial no. NCT04625725)[a]; risk reduction of hospitalization or death, 50%, (trial no. NCT04501978)[a]	(165,209)
BRII-196/BRII-198	02137.HK	Patients with mild-to-moderate COVID-19	Monoclonal antibodies, binds two sites of SARS-CoV-2 S protein	Requires verification (trial no. NCT04501978)[a]	(210)
DXP-593/ DXP-604	688235.SH	Patients with mild-to-moderate COVID-19	Monoclonal antibodies, binds two sites of SARS-CoV-2 S protein	Potential	(136)
REGEN-COV (Ronapreve)	Regeneron Pharmaceuticals, Inc., Roche	Patients with mild-to-moderate COVID-19	Casirivima B + Imdevimab monoclonal antibodies, binds two sites of	Risk reduction of symptomatic and asymptomatic COVID-19, 66.4% (NCT04452318)[a];	(130,211)

Table I. Continued.

B, Antibody-based therapy					
Name	Company	Indication	Mechanism of action	Effectiveness	(Refs.)
			SARS-CoV-2 S protein	risk reduction of hospitalization or death, 70-71% (trial no. NCT04425629)[a]	

[a]Primary endpoint of phase III study. N/A, not applicable; 3CL pro, 3-chymotrypsin-like protease; CYP3A4, recombinant cytochrome P450 3A4; S, spike; ACE2, angiotensin-converting enzyme 2; HSPGs, heparan sulfate proteoglycans; TMPRSS2, transmembrane protease, serine 2; IMPDH, inosine monophosphate dehydrogenase; eEF1A, eukaryotic translation elongation factor 1; TLR, toll-like receptor; B cell, bone-marrow cell; RBD, receptor binding domain; VEGF, vascular endothelial growth factor.

Protease inhibitors lopinavir and ritonavir were the first drugs used in clinical trials to target Mpro/3CLpro (87), the primary protease of SARS-CoV-2 that inhibits activation of IFN-α pathway and facilitates natural immune escape and massive viral replication (88). Although lopinavir/ritonavir had no significant therapeutic effectiveness for patients with COVID-19, they are more effective when combined with other drugs such as ribavirin and interferon (89). Drugs to inhibit Mpro, such as GC-376, PF-07304814 and PF-07321332, are in different stages of clinical trials to confirm their effectiveness and practicability for application worldwide (90,91). Paxlovid, an oral drug combined with PF-07321332 and nirmatrelvir, was released by Pfizer, US in 2021; it has a significant effect against COVID-19 and is used to treat adults and children aged >12 years with mild/moderate disease, as well as those at high risk of transforming to severe cases (92). Chloroquine and hydroxychloroquine, antimalarial drugs, are potential but controversial drugs in COVID-19 treatment. Biological studies have proven the effect of hydroxychloroquine on controlling viral load but clinical trials have reported side effects and no significant therapeutic benefit (93,94). High-dose chloroquine for COVID-19 treatment is not recommended due to its toxic side effects, including increased levels of liver enzymes, corrected QT level prolongation and increased death rate (95,96).

Umifenovir (Arbidol) is a broad-spectrum antiviral drug for treatment of influenza that targets the interaction between S protein and ACE2; it has been shown to inhibit membrane fusion, thereby inhibiting virus diffusion into host cells (97,98). Clinical data show that it is more effective compared with lopinavir/ritonavir (89,99), although certain clinical trials have shown contrary results on patients with mild/moderate COVID-19 (100). GeLactoferrin targets heparan sulfate proteoglycans to prevent viral attachment to cells (101). Studies showed that lactoferrin combined with remdesivir has effects against COVID-19 (102,103), providing a basis further investigation in the treatment of clinical cases. Camostat mesylate, developed for treatment of pancreatitis, has been revealed to block virus entry into lung cells (104).

Inhibitors of viral RNA include remdesivir (GS-5734), favilavir (T-705), molnupiravir (MK-4482/EIDD-2801), AT-527, merimepodib and PTC299; their effectiveness for COVID-19 treatment requires investigation (105). Remdesivir, a broad-spectrum antiviral medicine developed for Ebola virus infection, is the first drug to be accepted for clinical trials of COVID-19 treatment (106). The effect of remdesivir is unknown and the high price and intravenous (IV) route of administration prevent its widespread use (107). Molnupiravir is the first orally available drug for COVID-19 that has broad-spectrum anti-RNA virus activity. Early use of molnupiravir for COVID-19 outpatients decreases risk of hospitalization or death (108). AT-527 is also an orally available drug which need further investigation for COVID-19 treatment (109).

By inhibiting host proteins that support viral RNA, drugs such as plitidepsin, fluvoxamine and ivermectin, may be potential treatments for COVID-19 (100). Based on biological studies and mouse experiments (110,111), plitidepsin may exert greater antiviral effects than remdesivir and its safety has been proven in a number of cancer clinical trials (112,113). Fluvoxamine, an antidepressant, was previously suggested to be associated with decreased plasma levels of certain inflammatory mediators and to prevent viral infection of epithelial cells (114). Whether ivermectin decreases risk of SARS-CoV-2 infection is still uncertain and needs further investigation (115).

Convalescent plasma (CP), a blood-derived product obtained from patients who have recovered from COVID-19, has been shown to limit viral expression and modify the inflammatory response (116). It has proven to be an effective COVID-19 treatment by randomized controlled trials and retrospective studies and high-titer CP may have a more significant effect compared with low-titer CP (117,118). It is more effective in severely or critically ill patients with rapid progression of illness (119). The rate of adverse events is low, but there is still the possibility of enhanced infection mediated by antibodies and acute lung damage or allergic reactions associated with transfusion (120).

High-dose intravenous immunoglobulin (IVIg) is a blood-derived product from patients who have recovered from COVID-19 and is used as a treatment for severely and critically

ill patients (121). Patients with ARDS or those on mechanical ventilation support may benefit from IVIg137 treatment. This therapy is usually not used alone but combined with other therapies, such as CP and antiviral drugs, to obtain greater clinical effect (122).

Monoclonal antibodies (mAbs) have been shown to neutralize COVID-19 infection both *in vitro* and *in vivo* (123,124). Despite the problems of bioavailability, high cost and limited supply using current technology, they may have wider clinical applications due to their ability of self-replicate, which CP does not possess (125). Severely ill patients commonly present with overexpression of IL-6 and cytokine storms in their serology profile; therefore, the inflammatory response may be alleviated by decreasing expression of IL-6 (126). Tocilizumab and sarilumab, high affinity antibodies for IL-6 receptor that are commonly used to treat arthritis and cytokine release syndrome, decrease the inflammatory response in COVID-19 (127). Tocilizumab was found to have no notable benefit for moderately ill patients in terms of decreased risk of transition to severe illness or death, while a multi-center study of critically ill patients revealed that early use of Tocilzumab may contribute to extended survival period (128). REGEN-COV, a mAb cocktails of neutralizing antibodies casirivimab and imdevimab, has an effect on preventing the aggravation of COVID-19 and decreases risk of hospitalization and death for patients with COVID-19 in high-risk groups (129). In addition, subcutaneous injection of REGEN-COV is effective for post-exposure prophylaxis (130). Clinical trials have shown that REGEN-COV may have an antagonistic or synergistic action in combination with anti-inflammatory medications with diverse mechanisms of action; this requires further investigation (129). CT-P59, a fully human anti-SARS-CoV-2 mAb, has high binding affinity for RBD in S protein and prevents interaction with ACE2, which is key to prevent the virus from entering human cells (131). Experiments into the effect of sarilumab and bevacizumab on COVID-19 are ongoing (132,133). DXP-593 (based on SARS-CoV neutralizing mAb) had not meet the endpoint of validity on phase II trials and its action mechanism remains unknown (134,135).

Bamlanivimab (LY-CoV555/LY-CoV016, recombinant, fully human neutralizing IgG_1 mAb), sotrovimab (VIR-7831, fully human anti-SARS-CoV-2 mAb), REGN-10933, REGN-109876 and AZD1061 are effective against Omicron (136). In cell culture experiments, Omicron induces weaker neutralization by individual mAbs, thus contributing to immune escape (137-139). A trial investigating the effect of a panel of widely used mAbs against SARS-CoV-2 variants showed that combination of mAbs in low prophylactic doses is effective in preventing infection in mice (136), and high-dose REGEN-COV exhibits a notable therapeutic effect against Omicron infection (140). Although the mechanism SARS-CoV-2 variant immune escape remain uncertain, studies of mAbs indicate that identification of mAbs targeting highly conserved residues in viral S protein is key to avoid drug resistance and maintain effectiveness in treatment of COVID-19 variants (137,139).

Nanobodies (alpaca-derived antibodies), miniproteins (artificially designed proteins), human soluble ACE2 and ACE2 receptor traps can inhibit S protein and have shown potential therapeutic effects; owing to their diverse biological mechanisms, their effectiveness in treatment needs to be confirmed by clinical trials (81).

Corticosteroids relieve the inflammatory response caused by infection via anti-inflammatory and immunoregulatory effects (141). However, studies have shown conflicting results regarding its clinical effects (142-144). For dexamethasone, certain studies have shown decreased death rate and notable benefits especially in severely or critically ill patients receiving invasive mechanical ventilation (145,146), while other studies showed higher death rate and multiple organ dysfunction (147,148). In consideration of rebound phenomena, withdrawal reaction and side effects of corticosteroid therapy, short-term use (3-7 days) is recommended to begin within ten days for patients exhibiting rapid disease progression (144). Attention should also be paid to the dose of corticosteroids; excessive dose may lengthen the time of viral elimination owing to its immunosuppressive effect and induce adverse effects (144).

Active measures, such as prevention and treatment for complications, treatment for primary illness, prevention of secondary infection and timely application of organ function support, which are therapeutic principles for severe and critical cases, are also required (81).

Severely ill patients with arterial O_2 partial pressure/fractional inspired O_2 levels <300 mmHg should be provided with oxygen therapy immediately and close observation is required following oxygen inhalation by nasal catheter or mask (149). If respiratory distress and/or hypoxemia do not improve within 1-2 h, high-flow nasal cannula oxygen therapy or non-invasive ventilation should be adopted. Invasive mechanical ventilation should be considered if hypoxemia does not improve within 1-2 h or occurs with excessive breathing and tidal volume (150).

Airway management is required to improve humidification of the airway and use of active heating humidifier and close sputum aspiration are recommended. To promote sputum drainage and lung rehabilitation, airway clearance treatment should be performed as early as possible while maintaining stable oxygenation and hemodynamics (151). Extracorporeal membrane oxygenation should be applied as soon as possible when meeting the indications and with no contraindication (152).

Critically ill patients can develop shock as a complication. Vasoactive medication should be used in addition to adequate fluid resuscitation. Changes in blood pressure, heart rate and urine volume, as well as lactic and alkaline residue, must be closely monitored, and hemodynamic monitoring should be performed to guide infusion and use of vasoactive drugs to promote tissue perfusion (149).

Severely and critical patients may be associated with a prothrombotic state, which increases risk of life-threatening venous thromboembolism (153). Therefore, prophylactic use of anticoagulant therapy is recommended for patients with significantly increased levels of D-dimer with no contraindications.

Critically ill patients who present with acute kidney damage may need continuous renal replacement therapy. The balance of water-electrolyte and acid-base must be closely monitored for adverse events such as hypoperfusion and medication (154).

Adsorption, perfusion, plasmapheresis, blood/plasma filtration and other blood purification systems remove inflammatory components and minimize the cytokine storm; these serve as an early or middle-stage therapy for cytokine storm in severe or critical cases (155).

For COVID-19 child patients with multisystem inflammatory syndrome, multidisciplinary cooperation of management is required; treatment for early inflammation, shock, coagulation dysfunction, organ failure and infection should be administered as necessary. Patients with COVID-19 with typical or atypical Kawasaki disease phenotypes are treated similarly to the classic treatment regimen for Kawasaki disease, with IVIgG, glucocorticoids and oral aspirin being the most common treatment (156). Intestinal microecological regulators maintain intestinal microecological balance and prevent secondary bacterial infection (157).

Traditional Chinese medicine (TCM) is used to treat and prevent infectious disease, including COVID-19. TCM therapies have shown therapeutic effects at every stage of the disease with wide application and no reported cases of exacerbation, even in the epidemic caused by Omicron (158). In China, TCM therapies such as decoction, patent medicine and acupuncture are used by >90% of the population (159). In TCM, SARS-COV-2 is classified as 'epidemic disease' based on its transmission and clinical features. TCM divides the disease into medical observation and clinical treatment periods that are classified as four stages (mild, general, severe, critical) depending on the severity of disease. Numerous TCM principles and therapies are recommended in China and are usually combined with western therapies in clinical treatment to maximize therapeutic effect (160,161).

6. Measures to protect vulnerable groups: Vaccination

Vaccination may be the most effective method of overall long-term control of the novel coronavirus. Currently, development of effective vaccines is urgently required to decrease viral infection and provide protection for public health (162). A total of >100 vaccines have been developed based on a range of molecular platforms, such as DNA, mRNA in lipid nanoparticles, inactivated and live attenuated virus, protein subunits and recombinant vectors (163). A number of vaccines have exhibited good immunogenic effects in both clinical trials and real-world data (164,165). To March 2022, ten vaccines have been added to the World Health Organization Emergency Use Listing (EUL), while 20 new vaccines are undergoing EUL evaluation and prequalification (166).

mRNA-based vaccines include mRNA-1273 (Moderna) and BNT162b2 (BioNTech SE/Pfizer). The number of binding sites on SARS-CoV-2 S protein is associated with neutralizing antibody production; protein vaccines exhibit a similar association with neutralizing antibody response (167). mRNA-1273, a lipid nanoparticle-formulated mRNA vaccine that targets S protein of the novel coronavirus, induces a strong neutralizing antibody response (126). CVnCoV (CureVac) is a candidate mRNA vaccine that decreases strong T-cell responses and prevents viral replication in lung of hamsters exposed to wild-type SARS-CoV-2 (168). However, a phase IIb/III trial reported an overall efficacy of 48.2% in all stages of disease and all age groups, which was lower than expected (169). ARCT-154 (Arcturus Therapeutics), the first self-amplifying RNA vaccine, is the third mRNA the third most effective vaccine after Pfizer/BioNTech SE and Moderna. It uses viral self-replicating behavior to continuously express viral protein in large quantities. Compared with conventional mRNA vaccines, ARCT-154 express higher levels of S protein and induces increased production of neutralizing antibodies, stronger T cell response and T helper cell 1 and 2 immune responses (170). However, this self-replication is difficult to control and RNA interference may be required to inhibit overexpression of viral protein (162). A clinical trial in Vietnam showed that ARCT-154 met its immunogenicity primary endpoint and remains effective against Delta and Omicron with a protection rate of 95.3% in severe cases (170).

Inactivated virus vaccines, such as BIBP-CorV (Sinopharm) and CoronaVac (Sinovac Biotech), target the whole virus, while other types of vaccines use S protein as a target antigen. A clinical trial in China has shown high neutralizing antibody production with a low rate of adverse effects induced by inactivated vaccines WIBP and BIBP and protective efficiency >72% in a successful phase III trial (171). Recently, a cohort study in Singapore involving 52,709,899 people double-vaccinated with mRNA1273 (23% of participants), BNT162b2 (74%), CoronaVac (2%) or BIBP-CorV (1%) showed that the effectiveness of mRNA vaccines (mRNA1273 and BNT162b2; 96 and 90% efficiency, respectively) was higher than that of inactivated virus vaccines (BIBP-CorV and CoronaVac; 84 and 54% efficiency, respectively) (172).

Against the prevailing variant strains, all vaccines exhibit notable efficacy against infection with good tolerability (163). People vaccinated with BNT162b2 or mRNA-1273 may exhibit the highest efficacy following full-course inoculation (173,174). A meta-analysis of real-world data (175) showed that the observed effectiveness of Pfizer/BioNTech was 91.2%, Moderna was 98.1% and CoronaVac vaccine was 65.7%. CoronaVac. AZD1222 mRNA vaccine also decreases the rate of severe infection caused by SARS-CoV variants.

Live-attenuated vaccines merit further investigation due to their low cost, strong immunogenicity and long-lasting immune effect. Δ3678 SARS-CoV-2, as a potential candidate for COVID-19 vaccine, has showed validity to a certain extent in mouse models (176). The Bacillus Calmette-Guérin vaccine has showed indirect protection against COVID-19 and live attenuated Varicella Zoster vaccine has proven to decrease risk of infection using multivariate logistic regression analysis (177). DNA vaccines include AZD1222/ChAdOx1 (Oxford/AstraZeneca), JNJ-78436735/AD26.COV2.S (Janssen/Johnson & Johnson), Ad5-nCoV (CanSino Biologics) and ChAdOx1nCoV19 (Covishield) (166). Protein subunit vaccines have also been investigated; S-Trimer (SCB-2019) may be a candidate as it induces neutralizing antibody responses and has an acceptable safety assessment result (178). ZF2001, a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine, is well-tolerated and induced a good immune effect in phase I and II trials and may be a candidate protein subunit vaccine (179,180).

Adverse effects of vaccines can be considered to indicate antigenicity and immunogenicity, implying effective induction of immune responses, and severe adverse events caused by vaccination are rare (181). Aside from normal short-term

effects such as fever, rash, weakness, nausea, vomiting, drowsiness, insomnia, pain and induration at injection site and lymphadenectasis similar to ordinary vaccines (182,183), the long-term side effects are unknown due to the short period of monitoring. People with strong immune responses may be susceptible to higher risk of autoimmune disease following vaccination, which is similar to other vaccines (184).

Adherence to hygiene guidelines is still required following vaccination because there is a delay between vaccination and optimal level of immunity; this differs between vaccines (185). Increased asymptomatic cases and emergence of variants increase risk of infection during development of vaccine-induced immunity, indicating the necessity of following hygiene guidelines (20).

Breakthrough infection of fully vaccinated people occurs in rapid spread of Omicron with high infectivity (186). Studies show that serum polyclonal antibody responses induced by vaccination or natural infection may be less effective against Omicron, which may account for immune failure and high levels of breakthrough infection with Omicron (187,188). Moreover, vaccine-induced protection decreases and while patients with breakthrough infections are more likely to have mild symptoms that do not require hospitalization compared with unvaccinated patients (189). Therefore, additional vaccine doses, changes in vaccine formulation or intervention should be adopted to when breakthrough infection cases increase, as well as further studying SARS-CoV-2 variants.

COVID-19 vaccines face challenges. Vaccines limit viremia and infection-associated syndromes via IgG response but do not involve IgA response in local mucosa, which is associated with virus transmission (163). Therefore, the possibility of transmission via droplets expelled from asymptomatic vaccinated patients cannot be ruled out and reinfection following vaccination is also a challenge (20,33). Global strategies are required for affordable global vaccination. Vaccine uptake presents a challenge owing to the poor public understanding and trust of vaccines and regional policies. Ethical and logistical considerations, such as clinical trials, distribution, prioritization, cultural, religious and political factors and regulation, are also challenges to achieving herd immunity (190).

7. Conclusion

To date, SARS-CoV-2 has been widespread in all regions with highly infectious Omicron variant posing a novel threat to global public health. Real-time guidance and epidemiological analysis should be shared to strengthen global cooperation against the epidemic. At present, the specific pathogenicity and response strategies of COVID-19 are uncertain, requiring further research.

Acknowledgements

Not applicable.

Funding

The present study was supported by The Traditional Chinese Medicine Science and Technology Development Plan Project of Shandong Province, China (grant no. 2019-0231).

Availability of data and materials

Not applicable.

Authors' contributions

ZQ, CH and YC conceived and designed the review, ZQ, CH, JZ and YS wrote the manuscript. YS and JZ prepared the figures. LZ and YC performed the literature search. LZ and CH revised it critically for important intellectual content. All authors have read and approved the final manuscript. All authors are responsible for all aspects of the work and approve the submission in its current form. Data authentication is not applicable

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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