REVIEW ARTICLE

An In-Depth Analysis of Covid-19 Medications and Vaccination with A Focus on Side Effects

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ABSTRACT

Background: A pandemic threat to public health has been posed by the SARS-CoV-2 outbreak. To deal with the severe situation caused by this outbreak, medications were used, but we weren't thinking about the potential negative effects. This review sought to evaluate the efficacy and safety of various medications in COVID-19 patients, as well as the present state of medications and their adverse effects.

Methods: Several literature and databases were searched and analysed properly from 2020 to 2022 to find the relevant databases on the usage of proper medications.

Results: During COVID-19, many antivirals, antibiotics, and conventional drug therapy were in high demand. Many antivirals, including Remdesivir and Ritonavir, were tried, but they had a number of adverse effects, including hypokalaemia, headaches, and nausea. Another issue with the use of drugs in this pandemic is antibiotic resistance. Since vaccines are relatively new, adverse symptoms like fever, discomfort, chills, tiredness, nausea/vomiting, headache, and insomnia have so far been reported.

Conclusion: This analysis outlines a progressive change in the medical community, where simple treatment procedures have shown to be more successful than those using many drugs, producing better patient results. This indicates a shift in medical practice toward more simplified and effective modes of care.

Keywords: COVID-19, Drugs, Side Effects, Treatments, Vaccines

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INTRODUCTION

The Coronavirus disease-19 (COVID-19), a highly transmissible disease, was first detected in Wuhan, Hubei province, China, in mid-January 2020. SARS-CoV-2 is genetically linked to the previously identified SARS-CoV virus. The world witnessed what a virus may do to humans during the emergence of the new Coronavirus (SARS-CoV-2). Coronavirus belongs to the Nidovirales order and is classified as a member of the Coronaviridae family. COVID-19 is caused by an RNA virus (ssRNA) with a diameter of 60–200 nm consisting of four structural proteins: spike protein, envelope protein, membrane protein, and nucleocapsid protein. SARS-CoV-2 has a coronavirus-like structure with spike protein on its outer surface (Figure 1 Inset). It is made up of a variety of polyprotein, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and auxiliary proteins.[1] In a host, a membrane-derived lipid bilayer envelops the helical nucleocapsid containing the RNA virus and the coronavirus surface viral protein spike, membrane, and envelope.

The virus and its variations often attack the respiratory system, causing symptoms such as breathing difficulty, coughing, exhaustion, and fever. It may also be related to neurological issues such as loss of smell and taste and cerebrovascular illnesses. However, it is still unclear whether the neurological consequences are the result of viral infections or immunological responses. COVID-19 causes serious consequences in immunocompromised people who have diabetes, cardiovascular disease, obesity, a psychological illness, or a history of organ transplantation. According to reports, it may also impact the kidneys, heart, liver, intestines, neurological system, and eventually lead to various organ damage.[2]

As there were no efficient drugs present to treat the disease, many trials and errors were made. Trials with Remdesivir, lopinavir and ritonavir etc., were done, and WHO recommended these medications, but a list of side effects has been documented in the patients. Moreover, a lot of Antibiotics were also used in this treatment decorum. Furthermore, the safety and efficiency of existing vaccinations against the SARS-CoV-2 variant of concerns (VOCs) is disputed. The COVID-19 vaccination campaign must be promoted globally, particularly in low-vaccination-rate nations, since it will be an effective method for reducing viral dissemination as well as the formation of new VOCs. The COVID-19 case fatality rate is not constant; it varies with population, time, other socio-economic factors, and nations' mitigation measures.[3] Vaccine reluctance has been found in certain areas, which might be another explanation for this never-ending epidemic.

Numerous medications and vaccinations used to combat this pandemic has been discussed in this review. To ensure a thorough knowledge, the vaccination safety, hesitation, and vaccine-related adverse effects are also highlighted.

METHODOLOGY

We looked for articles on COVID-19 and its therapy in a number of electronic databases, including Pub Med, Embase, Medline, and Google Scholar. We searched for the keywords like “COVID-19”, “Coronavirus disease 2019” “treatment”, “medication”, “vaccination” “drugs” and “side effects”. This review covered studies that provided information about COVID-19 medicine and side effects. This review was open to articles from 2020 to 2022 that were published in clinical trials, cohort studies, case-controlled studies, case series, case reports and other review articles. Articles that offered no patient-related information, featured opinions, letters, suggestions, or guidelines were omitted. We incorporated peer-reviewed articles on adverse effects of various medications and COVID-19 vaccine treatment that were published in various scholarly journals. Additionally, we didn't include abstracts or preprints that hadn't been peer reviewed. In this review, we only considered articles that were published in English.

FINDINGS AND DISCUSSION

Drugs used to treat COVID-19 infection

Antivirals

For the past two years, the COVID-19 pandemic has been wreaking havoc on millions of people's lives and livelihoods. There is no effective recognized treatment method (drugs), and the advent of various variants as well as a considerable percentage of mutations are worrisome. A wide range of repurposed medicines and steroids are commonly used to treat the condition. However, some major side effects have been reported. Microbiota-related coinfections were recently discovered in COVID-19 patients. The World Health Organization recently suggested two new medications to treat COVID-19 patients. For patients with severe and critical COVID-19, an oral medication called baricitinib has now been strongly suggested. In addition, a JAK inhibitor class is suggested for use with corticosteroids to decrease immune system overstimulation.

Sotrovimab, a monoclonal antibody medicine, has also been recommended by WHO for mild COVID-19 patients at high risk of hospitalisation (older, immunocompromised, unvaccinated). Vaccines and antivirals protect people from severe COVID-19 illness symptoms and consequences. In this framework, the emergency use of two antivirals, molnupiravir and nirmatrelvir, has been licenced, with five days of therapy reducing disease progression by 30% and 89%, respectively.[4] **Table 1** includes information on commonly used medications, their mechanisms of action, and clinical trial findings. **(Figure 1)**.

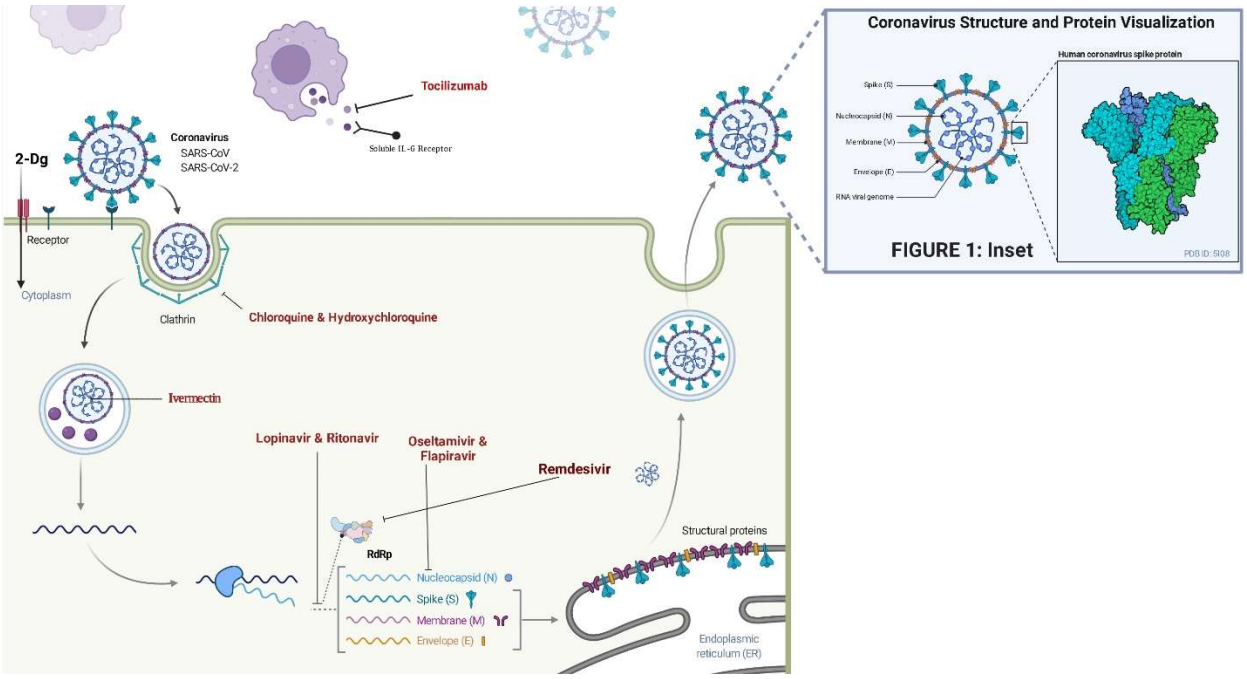

Figure 1: Viral entry and inhibition by antivirals and other category drugs. Inset: Structure and Morphology of SARS-CoV-2 virus. (Created with BioRender.com)

Antibiotics

Antimicrobial resistance is a secret danger lurking behind the COVID-19 pandemic, which has already taken thousands of lives before the worldwide breakout. A pandemic on the scale of COVID-19 has the potential to turn antimicrobial resistance into a double-edged sword, with the misuse of antibiotics having the potential to bring humanity back to pre-antibiotic times. Antimicrobial resistance has been ascribed to a variety of factors, including the extensive and unneeded use of antibiotics, which has aided the establishment and spread of resistant microorganisms. Various antibiotics, including azithromycin, doxycycline, tigecycline, clarithromycin, moxifloxacin, ceftriaxone, and ampicillin, were recommended for COVID-19 management. **Table 1** also provides an overview of the antibiotics used in COVID-19 and their side effects **(Figure 2)**.

Steroids

Physicians soon realized that circulating levels of the acute phase response proteins, C-reactive protein & serum amyloid A, were higher in oxygen-dependent COVID-19 patients, whereas pre-albumin levels were lower. These individuals also have higher pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-1-β, IL-2, IL-7, and IL-17 in their blood.[27] In severe COVID-19, the dysregulated interferon (IFN)-I response is likely to contribute to pathological damage to the lungs and other organs. In COVID-19 patients, aberrant up-regulation of neutralizing autoantibodies against type I IFNs may lead to severe illness by limiting type I IFNs' binding to their receptor downstream signaling.[28]

The rise in pro-inflammatory cytokines corresponds to the severity of the disease, and the higher the levels of IL-6 and TNF-, the greater the risk of mortality from COVID-19. While plasma levels of pro-inflammatory cytokines are greater in this case than in other cases of community-acquired pneumonia, they may be similar to those found in sepsis with acute respiratory distress syndrome (ARDS). In reality, the levels of circulating pro-inflammatory mediators varied a lot from study to study.[29] On the one hand, a comprehensive immunological examination of peripheral blood cells in severely ill COVID-19 patients revealed similar changes in sepsis.

Furthermore, there was significant heterogeneity in immune profiles among patients who mounted a lymphocytes response, with potentially three distinct immune responses, with strong activation of CD4 T cells (immunotype 1), mild activation of CD4 T cells (immunotype 2), or no detectable lymphocytes response (immunotype 3). Immunotype 1 was linked to a more severe COVID-19 infection.

Pleiotropic effects of corticosteroids are caused by a variety of biological pathways, including non-genomic and genomic effects. The molecular basis for the advantages of corticosteroids in severe infections has recently been outlined. In a nutshell, glucocorticoids reduce inflammation by increasing the production and release of anti-inflammatory proteins while blocking the production and release of pro-inflammatory proteins. Glucocorticoids bind to the glucocorticoid receptor (GR), which can be found in the cytoplasm of almost every cell. The GR dissociates from chaperone proteins heat shock proteins 70 (Hsp70), Hsp90, and immunophilin when it binds to glucocorticoids.[30]

Table 1: Descriptions of the different types of drugs used in COVID-19 management and their side effects

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
Antiviral				
Molnupiravir	Antiviral Oral medication	Molnupiravir is an analogue of ribonucleosides. It blocks the replication of SARS-COV-2 variants' nuclear matter.	Interim analysis, Phase 3 of the trial, showed that it lowered the risk of hospitalisation or mortality by roughly 50%. 7.3 percent of molnupiravir-treated patients were hospitalised or died (through Day 29), compared to 14.1 percent of placebo-treated patients. Approved by FDA[4].	Headache, Nausea, Rhinorrea
Remdesivir	Antiviral drug	Remdesivir's active form is a neucleoside analogue. It suppresses the function of RNA dependent RNA polymerase in SARS-COV-2.	1. In a 584-patient randomised control trial, 191 received a 5-day remdesivir course, 193 received a 10-day remdesivir course, and 200 received standard-of-care treatment. There were 9 deaths, with two deaths from the 5-day remdisivir group, three from the 10-day remdisivir group, and four from the SOC group[4].	1. Hypokalemia, Headache, Nausea. Respiratory failure with organ dysfunction especially low albumin, potassium, red blood cell count, platelet count (which aids in clotting), as well as yellow skin discoloration. Gastrointestinal discomfort elevated levels of transaminases (liver enzymes) in the blood significant injection site reaction Nausea, vomiting, sweating, and chills are all symptoms of low blood pressure. Increased level of liver enzymes, as detected by abnormal liver blood tests People taking remdesivir had increased amounts of liver enzymes, which could be a symptom of inflammation or impairment to liver cells. 2. Hypokalemia, Headache, Nausea.
Ritonavir-Lopinivir Combination:	Antiviral: protease inhibitor	1) HIV-1 protease inhibitors, combination of Ritonavir & Lopinivir used to bind SARS-Cov-3c (C30 endopeptidase) like protease that cleaves Coronavirus polyprotein[5]. 2) Ritonavir is a HIV protease inhibitor routinely prescribed to HIV patients that also potently inactivates cytochrome P4503A4 (CYP3A4), the major human drug-metabolizing enzyme. By inhibiting CYP3A4, ritonavir increases plasma concentrations of other anti-HIV drugs oxidized by CYP3A4 thereby improving clinical efficacy.	At the height of the pandemic, Cao et al. performed an open-label RCT at a specific hospital in Wuhan, China. They enrolled 199 hospitalised people having COVID-19 pneumonia with oxygen saturations of 94% on ambient air and randomly assigned them to either LPVr 400mg/100mg twice daily for 14 days (n=99) or standard therapy (n=100). The two groups had identical baseline characteristics. The primary outcome of time to clinical improvement (16 days in both groups; hazard ratio 1.31; 95 percent CI: 0.95 to 1.85; p=0.09)	Diarrhea Nausea Increased Alanine-amino-transferase (ALAT) 3-5 times more than normal. (High Dose Lopinavir/ Ritonavir Does Not Lead to Sufficient Plasma Levels to Inhibit SARS-CoV-2 in Hospitalized Patients With COVID-19) QTc prolongation[7,8].

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
			demonstrated no difference between the two arms after 28 days of ITT analysis[6]. In SARS-CoV-2 patients, the effectiveness of lopinavir/ritonavir with or without ribavirin is being studied in randomised controlled studies. This combination has currently been shown to have little benefit in elderly people with acute COVID-19. Despite protease inhibitors are a common category of drug used to treat HIV-1 infection, their usefulness in COVID-19 infections is questionable. Furthermore, numerous anti-HIV PIs have been shown to affect additional intracellular pathways. HIV protease inhibitors (indinavir, saquinavir, and lopinavir) have been shown to suppress lymphocyte death via altering mitochondrial homeostasis in the absence of viral infection. Given the lack of antiviral action of protease inhibitors, more research is needed to determine if the therapeutic effect is due to their anti-apoptotic rather than antiviral properties[7,8].As a result, even if the primary protease (3CLpro) in SARS-CoV-2 infected cells is the molecular target of lopinavir/ritonavir, there are no biochemical or molecular investigations verifying the interaction and correlating it with clinical efficacy of the protease inhibitor.	
Favipiravir	Antiviral drug	Flavipiravir suppresses SARS-COV-2 viral replication by specifically inhibiting RNA dependent RNA polymerase.	A significant clinical improvement in the Favipiravir group against the control group was observed within the first seven days following hospitalisation, according to a meta-analysis of six separate surveys (RR = 1.24, 95 percent CI: 1.09–1.41; P = 0.001, I2 = 0.0 %, P = 0.939)[9].	Diarrhea, Hyperuricemia, Teratogenicity
Ganciclovir	Antiviral drug	Ganciclovir (9-[(1,3-dihydroxy-2-propoxymethyl guanine) is a potent inhibitor of viruses. 2)inhibition of the replication of viral DNA by ganciclovir-5′-triphosphate (ganciclovir-TP). This inhibition includes a selective and potent inhibition of the viral DNA	Not Reported	Haematological changes are the most commonly observed unwanted effects, particularly neutropenia (about 40% of patients) and thrombocytopenia (about 20%), although these are usually reversible. Concomitant administration of granu-

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
		polymerase.		locyte-macrophage colony-stimulating factor (GM-CSF) may serve to moderate the depressive effects of ganciclovir on granulocyte production.
Antibiotics				
Azithromycin	Antibiotic (Macrolides)	Inhibits bacterial protein synthesis by binding to and interfering with the assembly of the 50S large ribosomal subunit and the development of the nascent polypeptide chain, similar to other macrolide antibiotics. In contrast to bigger macrocyclic antibiotics, it binds at the polypeptide exit tunnel, near to the peptidyl transferase centre (PTC) on the 23S rRNA, but does not impede PT action. Because of azithromycin's basicity, it penetrates outer membranes faster and enters bacteria more effectively, increasing its action against Gram-negative bacteria.	1. In a study, 8970 Inpatient laboratory-confirmed COVID-19 and got hospital admissions.735 Received hydroxychloroquine and azithromycin & 211 Received azithromycin alone. 2. A total of 55 patients were compared in the control group, who received hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r), to 56 patients in the case group, who got AZM in addition to the same regimen. Patients having a history of heart illness were not allowed to participate in the trial. Patients in the case group were also evaluated for cardiac arrythmia risk using the American College of Cardiology (ACC) risk assessment for AZM and HCQ usage. 3. The median age of the 2,541 patients was 64 years (IQR: 53–76 years), with a median total hospitalisation stay of 6 days (IQR: 4–10 days), 51 percent male, 56 percent African American, and a median time to follow-up of 28.5 days (IQR: 3–53). Overall, in-hospital mortality was 18.1 percent (95 percent CI: 16.6 percent –19.7 percent), with hydroxychloroquine + azithromycin accounting for 157/783 (20.1 percent [95 percent CI: 17.3 percent –23.0 percent]), hydroxychloroquine alone accounting for 162/1202 (13.5 percent [95 percent CI: 11.6 percent –15.5 percent]), azithromycin alone accounting for 33/147[10].	1.Diarrhea, Hypoglycemia, Cardiac arrest, Arrhythmia, QT prolongation. 2.Cardiovascular failure for lethal arrhythmia prolongation 3. Cardiac arrest, cardiopulmonary arrest 4. Except this Sultana et al.[11] reported Arrhythmiaa, Cardiac arrest Torsades de pointes, Atrioventricular block b,QT prolonged, Long-QT syndrome Ventricular fibrillation.
Tigecycline	Tetracyclines	The mechanism of action of some tetracyclines are quite similar to the action of tigecycline in which it behaves as an inhibitor of bacterial protein translation (i.e., elongation of peptide chain). The protein translation oc-	Not Reported	Vomiting and nausea are the mainstream adverse reactions. Some other common aftereffects include headache, diarrhea, dizziness and insomnia. But particular side effects of tigecycline in COVID-19 Patients

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
		curs on the 30S subunit of bacterial ribosomes via reversible binding to a helical region(H34). Tigecyclines have structural similarities to the tetracyclines. Tigecyclines have strong binding affinity and is bacteriostatic. Into the elongation of peptide chains the amino acid residues are incorporated and this is prevented by binding of tigecycline and results in loss of bacterial growth and peptide formation. The function of tigecycline was to overcome the molecular mechanisms of tetracycline resistance, by adding glycyclamide moiety to the 9th position of minocycline.Against many anaerobic organisms, gram positive and gram negative tigecycline shows broad spectrum of activity. Tigecycline is an analogue of minocycline. Active drug efflux and ribosomal protection confers resistance to the tetracyclines. And tigecycline exhibits both in vitro and in vivo activity against broad spectrum of bacterial pathogens.		are still not studied.
Moxifloxacin	Fourth generation fluoroquinolone[12]	To maintain the topology and function of the DNA molecule topoisomerase enzyme is required by bacterial chromosomes. Only two bacterial topoisomerases are relevant to fluoroquinolones, DNA gyrase and topoisomerases IV whereas there are four bacterial topoisomerases. The enzymes consist of pairs of two subunits and enzymes are tetramers[13]. In DNA gyrase, *GyrA* and *GyrB* subunits are present and in topoisomerase IV, *ParC* and *ParC* subunits are present[14]. Genes *gyrA* and *gyrB* encodes for the two DNA gyrase subunits and *parC* and *parE* genes encodes for the two topoisomerase IV subunits. Introduction of the negative supercoils into DNA is the main function of DNA gyrase whereas detachment of daughter chromosomes via mediation of a decatenation or catenation sequence is the main function of topoisomerase IV[13].	HCQ (400mg) and MOX (400mg) were started as empirical treatment in patients with a possible diagnosis of COVID-19.	QT prolongation, Increase in cTP -e interval. Except this, moxifloxacin carries the greatest risk of QT prolongation[15].

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
		Topoisomerase IV is mainly responsible behind the advancing replication fork. The event of replication-induced structural changes is avoided due to the presence of DNA gyrase. By attaching to a complex of DNA quinolones inhibit DNA synthesis and any of the two enzymes topoisomerase IV and DNA gyrase and pile at the attachment site. The DNA and RNA synthesis are blocked by the trapped complexes, which causes cell death. Both bacterial topoisomerase IV and bacterial topoisomerase II (DNA gyrase) are inhibited by moxifloxacin[13].		
Doxycyclin	Tetracyclin	Most antibiotics are bacteriostatic at low doses and bactericidal at high quantities, and doxycycline is no exception. By attaching to the 'A' site of the 30S ribosomal subunit and blocking the tRNA anticodon reading of bacterial mRNA, the antibiotic prevents bacterial protein production. Bacterial growth is stopped when protein synthesis is inhibited, allowing the host immune cells to lyse the bacterial cell[16] . Antibiotics normally only affect bacterial cells, not the cells of the host. Recent research has discovered that doxycycline attaches to and modifies the human 80S ribosome, reducing translation and specifically activating the cellular integrated stress response (ISR). Doxycycline was shown to target the 40S ribosomal subunit's helices h16 and h18, as well as H89 and residues near the peptidyl exit tunnel (PET) on the ribosomal 60S subunit, which did not coincide with the binding sites of any known translation inhibitors. Due to the evolutionarily conserved similarities between the bacterial and mitochondrial ribosomes, doxycycline has been found to interfere with mitochondrial protein synthesis, resulting in mitochondrial protein imbalance. This mitochondrial protein imbalance inhibits mitochondrial formation, which	A review done by Narendrakumar et al. 2021[17].	Esophagitis, esophageal ulceration, and mediastinitis.

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
		has been exploited as a novel therapeutic method to target cancer cells since cancer cells lacking mitochondria have been found to be more vulnerable to cytotoxic medicines.		
Carbapenem	Member of β-lactam family.	Carbapenems enter through porin or outer membrane proteins (OMPs), in gram-negative bacteria. Carbapenems acylate the penicillin-binding proteins (PBPs) permanently, once carbapenems enters the periplasmic space. Carbapenems inhibit peptidase reactions as well as peptide cross linking and for peptidase domain of PBPs it functions as mechanism-based inhibitors [18]. They have the potential to bind to multiple different PBPs.	Not Reported	Not Reported
Vancomycin	It is a tricyclic glycopeptide antibiotic	The mechanism of action of vancomycin is inhibition of peptidoglycan biosynthesis. Gram positive bacteria contains thick peptidoglycan layer and have multiple skeletons of N-acetylmuramic and N-acetylglucosamine amino sugars. A high-level resistant polymeric chain is formed by lateral short peptide residues. The drug blocks the linkage to the glycopeptide polymer when it binds with C-terminal D-alanyl D-alanine residues to inhibit polymerization. The drug prevents its binding to the growing tip of the peptidoglycan.	Vancomycin should be avoided in Myasthenic gravis infected patients in SARS-CoV-2.	Not Reported
Cephalosporin	Cephalosporins are group of β-lactams. The drug has four generations of ephalosporins.	Cephalosporins binds to penicillin binding proteins (PBPs) enzyme and synthesis of peptidoglycan layer is disrupted. For synthesis of bacterial cell wall these enzymes are necessary.	The risk of death in SARS patients who took cephalosporin and some broad-spectrum antibiotics was 13%. The 3rd generation cephalosporin, ceftazidime was given to the patients in a dose of 1000mg 3 times daily for 5 days, it was observed that the duration of symptoms and recovery time reduced in moderate and severe patients.it was more helpful to the patients with only two medications (dexamethasone + either ceftazidime or cefepime)[19].	Not Reported
Other Medications				
Dexamethasone	Corticosteroid	Dexamethasone blocks proinflammatory	A total of 2104 individuals with covid 19 were	Appetite loss, mood swings, agitation, and

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
		genes that code for inflammatory markers such as chemokines, cytokines, and cell adhesion molecules [CAM], lowering the cytokines storm that occurs with covid 19 viral infection.	randomised to receive Dexamethasone in a Randomized Control Trial, whereas 4321 were assigned to take standard therapy. Within 28 days following randomization, 482 patients (22.9%) in the Dexamethasone group and 1,110 patients (25.7%) in the standard treatment group died[20].	headaches Potentially higher blood glucose levels (hyperglycaemia) are temporary. Prolonged use (I.e., used for more than two weeks) may be associated with adverse events such as glaucoma, cataract, fluid retention, hypertension, psychological effects (e.g., mood swings, memory issues, confusion or irritation), weight gain, or increased risk of infections and osteoporosis.
Methylprednisolone	Corticosteroid	Methylprednisolone disrupts the cytokine cascade, inhibits T cell activation, and reduces immune cell extravasation into the central nervous system, reducing inflammatory effects in covid patients.	A total of 83 covid patients were administered methylprednisolone in a randomised control trial, while 90 patients were not given methylprednisolone. Nine patients (10.84 percent) in the methylprednisolone group died, while 24 patients (26.67 percent) in the non-methylprednisolone group[21].	Agitation, Transaminase elevation, Hyperglycaemia.
Ivermectin	Antiparasitic drug	The active form of remdesivir is a nucleoside analogue. It inhibits RdRp activity in SARS-CoV-2.	A study of 21 patients was done and Six of the 21 persons were hospitalized for toxic effects from ivermectin use; all 6 reported preventive use, including the 3 who had obtained the drug by prescription[22].	Diarrhea
Tocilizumab	Interleukin -6 receptor inhibitor	Tocilizumab binds to both the mIL-6R and the sIL-6R receptors. Additionally, both classical and trans-signals are inhibited. Interleukin is also inhibited, reducing the cytokine storm.	In a 438-patient randomised control trial, 143 were given placebo and 295 were given Tocilizumab. After 28 days, the mortality rate in the Tocilizumab group was 24.41 percent (72/295), compared to 25.51 percent (36/143) in the placebo group[23].	Serious skin infections, Headache.
2-DG (2-Deoxy-D-glucose)	Antimetabolite, Anticancer drug	2-DG binds to SARS-CoV-2's binding site and inactivates it, preventing it from attaching.	In a phase 3 clinical trial with 220 covid patients, 42 percent of patients improved symptomatically and no longer required oxygen supplementation, whereas 32 percent of patients in the placebo group improved symptomatically[24].	Elevated blood glucose levels, Lethargy, Progressive weight loss.
Bamlanivimab	Monoclonal antibody	Bamlanivimab binds to the receptor binding site of the SARS-COV spike protein, preventing it from attaching to human ACE2 receptors.	In a control trail with 403 patients, the rate of 30 days hospitalization in covid patients who received Bamlanivimab was 7.2%, whereas it was 19-20% in patients who did not receive	Nausea, Headache, Diarrhea

Drug Name	Classification of Drugs	Mode of Action	Results of clinical trials	Side effects
			Bamlanivimab[25].	
Fluvoxamine	Selective Serotonin Reuptake inhibitor (SSRI)	Platelets lack enzymes that produce serotonin. When thrombosis begins, platelets use serotonin from the plasma to stimulate neutrophil recruitment. SSRIs reduce serotonin reuptake, which reduces neutrophil recruitment and cytokine storm. Fluvoxamine also works on mast cells, lowering histamine release and, as a result, the cytokine storm in covid sufferers.	A total of 152 individuals were included in a double-blind placebo-controlled clinical trial, with 80 receiving Fluvoxamine and 72 receiving placebo. 1.25 percent of patients (1/80) who got Fluvoxamine experienced major adverse events such as low oxygen saturation, fever, pneumonia, and so on, whereas 8.32 percent of patients (6/72) who received placebo experienced serious adverse events[4].	Headache, Gastroenteritis, dehydration
Hydroxychloroquine	Antimalarials	Interference with the endocytic pathway, sialic acid receptor blocking, limitation of pH-mediated spike (S) protein cleavage at the angiotensin-converting enzyme 2 (ACE2) binding site, and cytokine storm prevention.	1. In a study, 8970 Inpatient laboratory-confirmed COVID-19 and got hospital admissions.735 Received hydroxychloroquine and azithromycin & 211 Received azithromycin alone[26]. 2. A total of 55 patients were compared in the control group, who received hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r), to 56 patients in the case group, who got AZM in addition to the same regimen. Patients having a history of heart illness were not allowed to participate in the trial. Patients in the case group were also evaluated for cardiac arrythmia risk using the American College of Cardiology (ACC) risk assessment for AZM and HCQ usage. 3. The median age of the 2,541 patients was 64 years (IQR: 53–76 years), with a median total hospitalisation stay of 6 days (IQR: 4–10 days), 51 percent male, 56 percent African American, and a median time to follow-up of 28.5 days (IQR: 3–53). Overall, in-hospital mortality was 18.1 percent (95 percent CI: 16.6 percent –19.7 percent), with hydroxychloroquine + azithromycin accounting for 157/783 (20.1 percent [95 percent CI: 17.3 percent –23.0 percent]), hydroxychloroquine alone accounting for 162/1202 (13.5 percent [95 percent CI: 11.6 percent –15.5 percent]), azithromycin alone accounting for 33/147[10].	Headache, Dizziness, Loss of appetite.

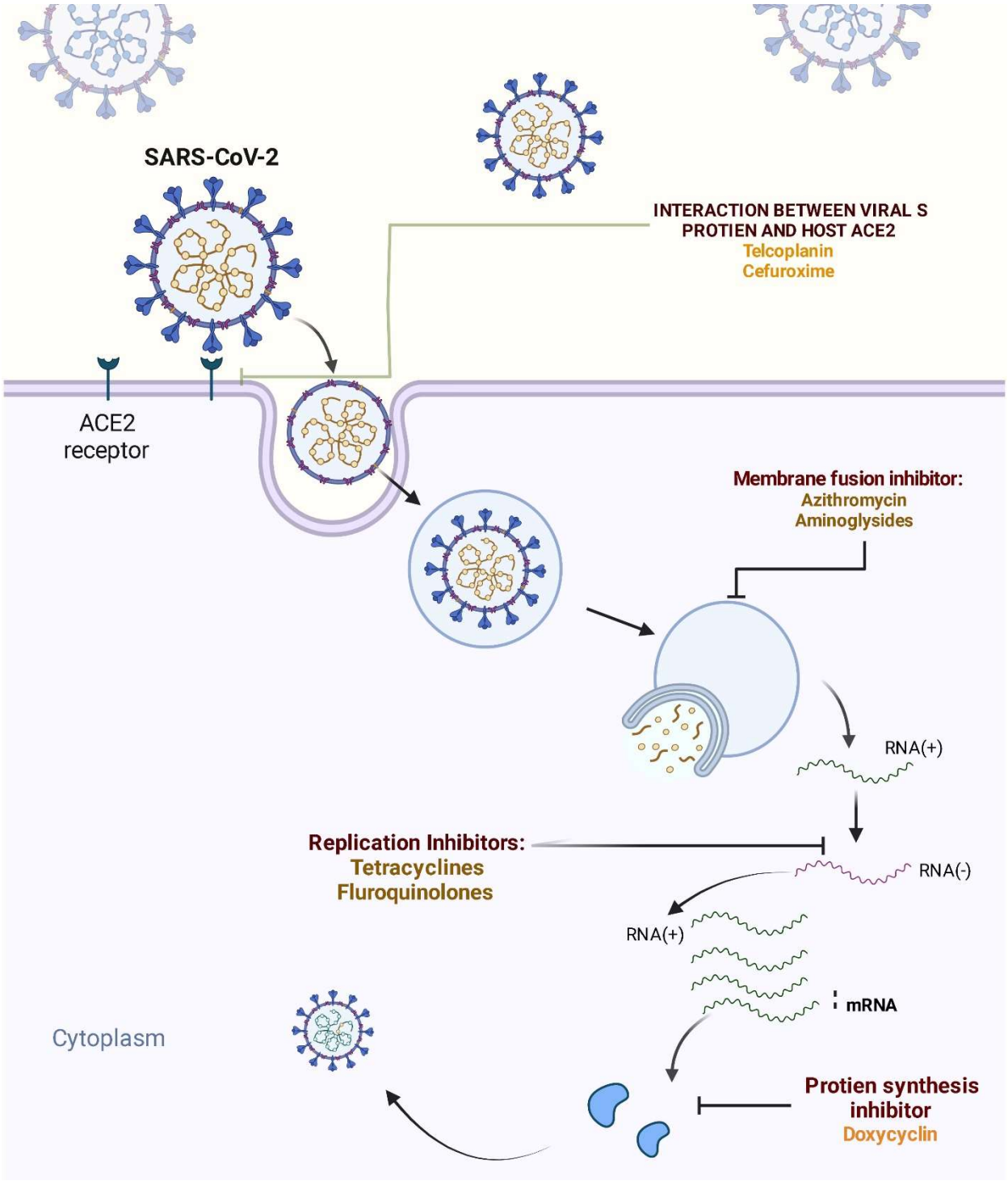

Figure 2: Mechanism of action of the antibiotics used in COVID-19 management. (Created with Bio-Render.com)

It then reaches the nucleus, where it interacts with particular DNA sequences (glucocorticoid responsive elements) in the regulatory area of target genes, resulting in chromatin remodeling. By blocking histone acetyltransferases & activating histone deacetylases, activated GR suppresses the expression of pro-inflammatory genes. Glucocorticoids, for example, suppress the expression of the interferon regulatory factor 3 (IRF3) transcription factor, which is involved in interferon synthesis and viral defense. Through increased expression of the inhibitory protein IB, the GR-glucocorticoid complex also suppresses the synthesis of pro-inflammatory proteins by sequestering nuclear factor-B (NF-B) inside the cytosol. glucocorticoid-induced leucine zipper (GILZ), an inhibitor of NF-B, and mitogen-activated protein (MAP) kinase phosphatase 1, an anti-inflammatory protein that suppresses nuclear translocation of transcription factor GATA-3 associated in T helper (Th)2 type cytokine expression, are both stimulated by glucocorticoids. They increase the formation of annexin 1, which inhibits the expression of phospholipase A2

and improves the resolution of inflammation and phagocytosis of apoptotic neutrophils by macrophages.[31]

Glucocorticoids limit leucocyte recruitment by suppressing the synthesis of acute-phase reactants, including chemokines.[32,33] They block the diapedesis of leucocytes by inhibiting the expression of endothelial-leukocyte adhesion molecule 1 (ELAM-1), intracellular adhesion molecule 1 (ICAM-1), and vascular adhesion molecule 1 (VCAM-1). (1) myeloid cells: macrophages, monocytes, tissue-resident, migratory, as well as plasmacytoid dendritic cells (DC), and granulocytes; (2) lymphocytes: CD8, Th1, Th2, and Th17, as well as Treg and B cells, are all targets for glucocorticoids. Glucocorticoids inhibit leucocyte maturation, differentiation, and proliferation in all subtypes. They cut down the number of monocytes/macrophages, DC, and granulocytes from eosinophils and basophils.

Glucocorticoids stimulate the neutrophil release and demargination from the bone marrow, as well as the anti-inflammatory cytokines IL-10 and transforming growth factor β (TGF-β) secreted by DCs. They suppress antigen presentation to T lymphocytes by lowering the membrane expression of MHC class II and Fc receptors.[34]

B cell lymphocyte activation, proliferation, and immunoglobulin production are all inhibited by glucocorticoids.[34] Apoptosis is used to eliminate thymic stromal cells and T cells. They cause naive T-cells to polarise toward anti-inflammatory Th 2 and T-reg phenotypes, preventing them from polarizing toward pro-inflammatory Th1 and Th17 phenotypes. Glucocorticoids then decrease lymphocyte production of pro-inflammatory cytokines such as IL-2, IL-4, IL-5, IL-13, and IFN. **Table 1**[22–25,35–38] additionally lists the side effects of different types steroidal drugs of as well as their way of actions.

Other Drugs

Apart from antibiotics and antivirals, a variety of other medications were used to treat COVID-19. **Table 1** also provides an overview of these drugs and their potential side effects **(Figure 2)**.

Vaccines in immunization against COVID-19

Most countries are dealing with a vaccination hesitancy problem, in which people are hesitant to take vaccines due to worries about both short- and long-term safety. Long-term vaccination safety would probably necessitate more large observational studies, which could lead to increased vaccine uptake. Except for the Ad26.COV2S vaccine developed by Janssen pharmaceuticals in the United States showed 66.9% efficacy in phase III clinical trials. More than 70% efficacy was observed among the vaccines now available.[39] Sputnik V, mRNA-1273/Moderna, and BNT162b2/Pfizer/BioNTech vaccines all showed more **(Table 2)** than 90% vaccination effectiveness.

Injection site pain, tiredness, myalgia, chills, and nausea were common AEs. Lymphadenopathy, herpes zoster, appendicitis, myocarditis, and facial palsy were the most significant adverse events reported after receiving the BNT162b2/Pfizer/BioNTech vaccine. Even though more than 80% of the infections were asymptomatic, moderate, and self-limiting, older patients and those with underlying chronic conditions succumbed or required ICU treatment and hospitalizations.

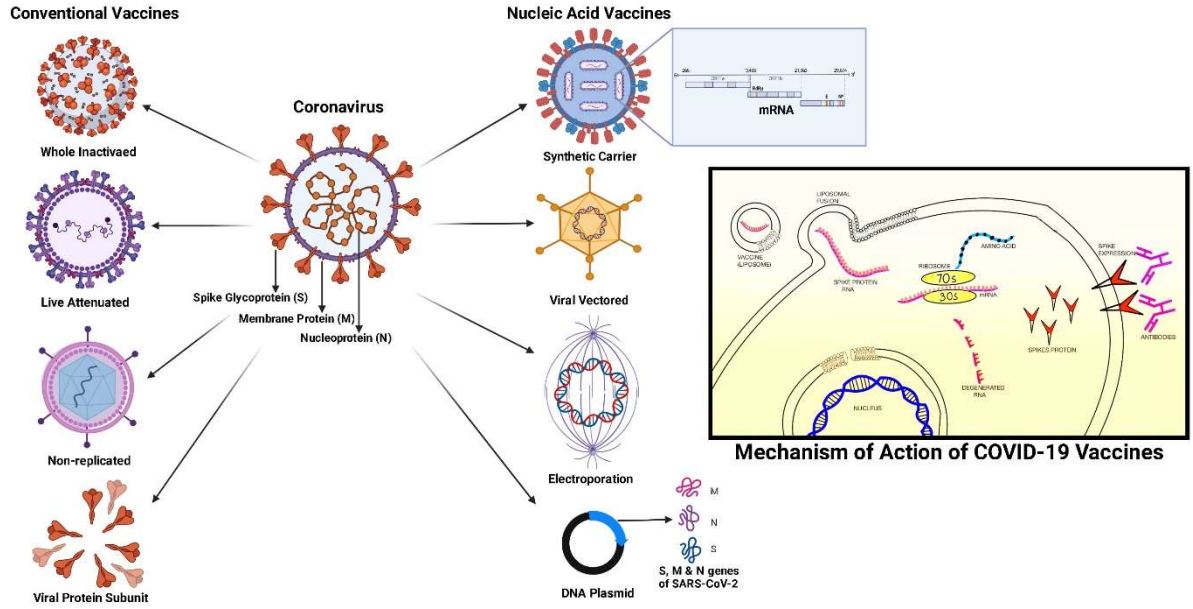

Figure 3: COVID-19 vaccines and their possible mode of action. (Created with BioRender.com)

Table 2: Descriptions of the vaccines used in COVID-19 immunization and their side effects

Vaccine /Strain Name with the Manufacturer/Developer	Type of Vaccine	Route of Administration, Dose: Single/ Booster	Pre-clinical Trial Data	Current Status	Side Effects	Efficacy/ Immunogenicity
AZD1222/ ChAdOx1nCoV−19/ Covishield (Oxford University and AstraZeneca, UK/ Serum Institute of India)	Virus vector: non-replicating simian adenovirus vector ChAdOx1	Intramuscular, Single, Booster	Available	The Phase III clinical trial in the United Kingdom, the MHRA, and the CDSCO in India had all cleared it for emergency use. This is in WHO Emergency Use List	The Phase III clinical trial in the United Kingdom, the MHRA, and the CDSCO in India had all cleared it for emergency use. This is in WHO Emergency Use List[4,39].	70.4% (64.1% after single dose) efficacy
Sputnik V (Gamaleya research institute, Russia	Virus vector: Adenovirus type 5 (rAd5) and adenovirus type 26 (rAd26) are non-replicating viral vectors (rAd26)	Intramuscular, Booster	Not available	Phase III clinical trial, CDSCO, India had accepted its emergency use.	Fever, pain, chills, exhaustion, nausea/ vomiting, headache, sleeplessness, lymphadenopathy, erythema, pruritus, edema, and diarrhoea[4,39].	91.6%
mRNA−1273/Moderna (Moderna/NIAID, USA)	mRNA encapsulating a stable S protein in lipid nanoparticles	Intramuscular, Booster	Available	Phase III clinical trial, CDSCO, India accepted for its backup use, WHO Emergency Use Listing.	Fatigue and headache[4,39]	94.1% efficacy
. BNT162b2 (Pfizer/BioNTech/Fosun, USA)	Nucleoside-modified mRNA encapsulated in lipid nanoparticles	Intramuscular, Booster	Available	Phase III clinical trial, authorized for use under an EUA by the FDA, WHO Emergency Use Listing	Moderate pain at the site of injection, fatigue, and mild headache with Lymphadenopathy, herpes zoster, appendicitis, myocarditis, Facial palsy[4].	89.7%
. NVX-CoV2373 (Novavax, USA)	Trimeric SARS-CoV−2 S protein nanoparticle plus Matrix-M1 adjuvant	Intramuscular, Booster	Available	Phase III clinical trial	Tenderness & pain at the site of injection, muscle pain, moderate fatigue [4,39]	77.8% (65.2% against delta variant)
Covaxin/BBV152 (Bharat Biotech in collaboration with the Indian	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, CDSCO/ ICMR, India, and	Mild Headache, associated with fever, fatigue, and muscle pain	NA

Vaccine /Strain Name with the Manufacturer/Developer	Type of Vaccine	Route of Administration, Dose: Single/ Booster	Pre-clinical Trial Data	Current Status	Side Effects	Efficacy/ Immunogenicity
Council Medical research (ICMR), and National Institute of Virology (NIV), India)				the WHO had approved its emergency use.		
CovaxinBBV154 Intranasal (vaccine candidate) (Bharat Biotech, India)	Adenovirus vector with ChAD SARS-CoV−2-S strain	Intranasal	Not Available	Pre-clinical trials	NA	NA
BBIBP-CorV/19nCoV-CDC-Tan-HB02 (HB02) strain (Beijing Institute of Biological Products/ Sinopharm, China)	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, WHO Emergency Use Listing	Data of phase I and II: Pain at Injection site mild fever, headache, self-limiting, no serious adverse effects	Seroconversion100% & efficacy 78.1%
WIV04 strain (Wuhan Institute of Biological Products/ Sinopharm, China) vaccine Booster	Whole cell inactivated	Intramuscular	Not available	Phase III clinical trial	pain at Injection site, headache	72.6%
CoronaVac/PiCoVac (Sinovac, China)	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, emergency use approved in China, WHO Emergency Use Listing	Pain at Injection site, fatigue, myalgia, chills,nausea	83.5%
.Ad5-nCoV (CanSino Biological Inc./Beijing institute of biotechnology, China)	Virus vector: a non-replicating, adenovirus type 5 (Ad5)-vector	Intramuscular, Single	Not available	Phase III clinical trial	Fever, fatigue, headache, muscle pain	Phase III trial results have not yet been published.
ZF2001 (Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical, China)	Recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001)	Intramuscular, booster	Not available	Phase II clinical trial	Fever, headache, cough, injection site pain, swelling, redness, and fatigue[4,39].	83% in 2 doses and 97% after third dose
Ad26.COV2·S (Janssen pharmaceutical, USA)	Virus vector: a non-replicating, adenovirus type 26 (Ad26)-vector	Intramuscular, Single	Available	Phase III clinical trial, WHO Emergency Use Listing	Injection site pain, fatigue, myalgia, nausea[4,39]	66.9%

Most early therapeutic efforts relied on repurposed pharmaceuticals, convalescent sera or monoclonal antibodies to treat significant COVID-19 patients because there were no antiviral medications available at that time. People all across the world are getting vaccinated as a result of vaccine discovery, manufacture, approval, and availability.

Immunization by viral vector with spike protein-containing mRNA has raised concerns about vaccine efficacy and safety, which has stoked widespread vaccine scepticism. Most vaccine candidates approved for emergency administration by the WHO, the USFDA, and local regulatory agencies were still in phase III clinical trials, with little information available in the public domain about safety, efficacy and long-term implications **(Figure 3)**.

Conclusion

Multiple waves of the current COVID-19 pandemic have impacted various countries of the entire world in the previous two years, causing significant illness and mortality. A large number of SARS-CoV-2 variations continue to arise, with some appearing to be more transmissible and less susceptible to virus-specific immune responses. As a result, scientists, researchers, medics, and a variety of government organizations are under intense pressure to figure out how to combat it. There have been numerous medications used in the fightback. There is some hope for now, but we should keep in mind the potential side effects of these medications.

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