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REVIEW

COVID-19 therapy and vaccination: a clinical narrative review

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Abstract

The SARS-CoV-2 pandemic is the most globally impacting health issue our world has faced over the last century. As of January 7, 2022, around 300 million cases have been reported worldwide, with over 5 million deaths. The SARS-CoV-2 infection causes a hyperactive host immune response leading to an excessive inflammatory reaction with the release of many cytokines — cytokine storm — commonly noticed in acute respiratory distress syndrome, sepsis and fulminant multiorgan failure. Since the beginning of the pandemic, the scientific medical community has worked on therapeutic procedures that interfere with the exaggerated immune response. Thromboembolic complications are widespread in patients who are critically ill with COVID-19. Anticoagulant therapy was initially considered a cornerstone in hospitalized patients and even in the early post-discharge period; however, later trials have aborted the clinical benefits except for suspicion of or confirmed thrombosis. Immunomodulatory therapies are still crucial in moderate to severe COVID-19. Immunomodulator therapies include various medications from steroids to hydroxychloroquine, tocilizumab and Anakinra. Anti-inflammatory agents, vitamin supplements and antimicrobial therapy had initial encouraging evidence, but there are limited data to review. Convalescent plasma, immunoglobulins, eculizumab, neutralizing IgG1 monoclonal antibodies and remdesivir have positively impacted inpatient mortality and hospital length of stay. Eventually, wide population vaccination was proven to be the best tool to overcome the SARS-CoV-2 pandemic and help humanity return to regular life. Many vaccines and various strategies have been used since December 2020. This review discusses how the SARS-CoV-2 pandemic has progressed and surged, and summarizes the safety and efficacy of the most used therapies and vaccines in the light of recent evidence.

Keywords: convalescent plasma, COVID-19, eculizumab, immunoglobulins, neutralizing IgG1 monoclonal antibodies, remdesivir, SARS-CoV-2, steroids, tocilizumab.

Citation

Chinta S, Rodriguez-Guerra M, Shaban M, Pandey N, Jaquez-Duran M, Vittorio TJ. COVID-19 therapy and vaccination: a clinical narrative review. *Drugs Context*. 2023;12:2022-7-2. https://doi.org/10.7573/dic.2022-7-2

Introduction

The world has been facing the most challenging pandemic of the modern era. The SARS-CoV-2 infection causes COVID-19, affecting over 450 million people worldwide. COVID-19 is characterized by the overexpression of inflammatory markers such as interleukins. The widespread dysregulated host immune response can result in multiorgan failure, thromboembolism and death. Immunomodulatory agents and systemic anticoagulation were believed to provide clinical benefits against disease progression and thromboembolic complications if started in the selected groups depending on case severity and hospitalization status.[1]

Review

SARS-CoV-2 mechanism of action

Coronaviruses have been the focus of concern since the beginning of the twenty-first century due to the outbreaks of three coronaviruses, with the initial outbreaks being MERS-CoV in 2012 and SARS-CoV in 2003.[2] The first genome sequence of SARS-CoV-2 was published

on January 10, 2020. The outbreak of COVID-19 in China peaked in February 2020.[3] SARS-CoV-2 differs from the other older versions of coronaviruses by the site of infection transmissibility.[2] During the initial waves of the COVID-19 pandemic, ethnic minorities were more susceptible to infection and demonstrated poorer outcomes in terms of morbidity and mortality due to sociocultural aspects of the pandemic; however, this observation was abolished in the later waves.[4] The large global outbreak of SARS-CoV-2 has seriously endangered healthcare systems worldwide. The sudden surge of SARS-CoV-2 has revealed the shortage of critical care medicine resources and intensivists.[5]

The spike (S) protein is key to the fast spread of SARS-CoV-2. The virus efficiently binds to the angiotensin-converting enzyme 2 (ACE2) receptor with the S protein. ACE2 receptors are highly abundant in the bronchi, lung parenchyma, heart, kidney and gastrointestinal tract, contributing to the complex and variable presentations in acute SARS-CoV-2 infection.[6] Following ACE2–S protein binding, the cellular transmembrane protease serine 2 (TMPRSS2) primes the S protein to allow the virus to enter host cells through clathrin-dependent endocytosis. The virus alters the behaviour of host cells and tissue, making them unable to fulfil their normal function by hijacking the endogenous transcriptional machinery.[6] In addition, multiorgan failure in severe COVID-19 infection is directly associated with the cytokine release syndrome rather than with active viral replication. Patients with SARS-CoV-2 have lymphopenia, mainly related to the significant reduction in absolute T cell counts, particularly cytotoxic T lymphocytes ($CD8^+$), increased neutrophil counts, and elevated levels of pro-inflammatory cytokines, especially IL-2, IL-6, IL-10 and IFNγ. The cytokine storm is associated with the activation of coagulation factors predisposing to the hypercoagulable status related to the considerably worsening multiorgan failure.[7]

Compared with previous strains of coronaviruses, SARS-CoV-2 has significantly worst post-recovery implications. The mutations in the initial SARS-CoV-2 strain had been a significant cause of mortality and uncontrolled virulence. SARS-CoV-2 exhibited deleterious impacts on systems other than the respiratory system (primary target organ) such as the central nervous, haematological, hepatic, renal and endocrinal systems.[8]

During the initial period of the outbreak of COVID-19, sequence-based analyses suggested the horseshoe bat as the natural reservoir, and primary pieces of evidence prompt Malayan pangolin as an intermediate host.[9] The S protein plays a crucial role in determining the host range. Analysis of the S protein receptor-binding domain (RBD) has revealed that SARS-CoV-2 and Malayan pangolin CoV share identical binding residues to ACE2.[10] The SARS-CoV-2 virus belongs to lineage B of betacoronaviruses, demonstrating a robust phylogenetic similarity with the BatCoVRaTG13 type. S glycoprotein projections of two subunits, S1/S2, provide a unique crown-like formation (corona) on the virion surface. S1 is primarily the RBD, whereas S2 functions in the virus–cell membrane fusion mechanism.[11] Mutations in the viral genome are reported in multiple genomic regions even though SARS-CoV-2 possesses unique proofreading activity for nascent RNA. The human antiviral defence mechanisms, such as adenosine deaminase acting on RNA (ADAR) and apolipoprotein B mRNA-editing enzyme (APOBEC), are also suspected of contributing to SARS-CoV-2 mutations.[10]

Delta variant

The SARS-CoV-2 B.1.617 variant was identified in October 2020 in India. It includes three subtypes: B1.617.1, B.1.617.2 and B.1.617.3, which have variable mutations in the N-terminal domain (NTD) and the RBD of SARS-CoV-2 S protein that facilitate the evasion capability of these variants. The Delta variant spreads faster than other variants and can escape the neutralization by monoclonal antibodies targeting NTD and RBD such as bamlanivimab.[12] Sera collected from convalescent individuals up to 12 months after symptoms were four-fold less potent against the Delta variant than the Alpha variant (B.1.1.7).[12]

Sera from individuals who had received a single Pfizer or AstraZeneca vaccine dose had a barely discernible inhibitory effect on the Delta variant. However, a second dose of either has developed a satisfactory neutralizing response in 95% of individuals, though with lower effectiveness against the Delta variant than against the Alpha by three-fold to five-fold. The spread of the Delta variant is associated with an escape from antibodies that target non-RBD and RBD epitopes of the S protein.[12,13]

Omicron variant

On November 26, 2021, WHO designated the new SARS-CoV-2 strain — named Omicron, from the letter 'όμικρον' in the Greek alphabet — as a variant of concern (B.1.1529 variant). This new variant is potentially associated with high transmissibility, leading to high infectivity and increased reinfection rates.[11] The SARS-CoV-2 Omicron variant (BA.1/B.1.1.529) harbours up to more than 30 mutations in its S protein, the target of neutralizing antibodies. Given its potential to escape vaccine-induced humoral immunity, Garcia-Beltran et al.[14] measured the neutralization potency of sera from 88 recipients of either mRNA-1273, 111 BNT162b and 40 Ad26.COV2.S

vaccines against wild-type, Delta and Omicron SARS-CoV-2 pseudoviruses. They found that individuals boosted with mRNA vaccines exhibited potent neutralization of Omicron that were four-fold to six-fold lower than the wild type, suggesting enhanced cross-reactivity of neutralizing antibody responses despite Omicron pseudovirus infecting more efficiently than other variants tested.[14] The Omicron variant displays an unusual association of 30 mutations, 3 deletions and 1 insertion. Compared with the Delta variant, the RBD of Omicron has an increased electrostatic surface potential but a decreased affinity for the ACE-2 receptor. The NTD has reduced surface potential and a lower affinity for lipid rafts. The Omicron variant is less fusogenic and thus less pathogenic than Delta due to a restructuring of the S1–S2 cleavage site. These changes suggest that Omicron does not have any considerable advantage over the Delta variant in terms of infectivity. However, in Omicron, neutralizing epitopes are greatly affected, meaning that current vaccines will probably confer little protection against this variant.[15]

To test the potential durability of immunity against SARS-CoV-2 variants, Wang et al.[5] evaluated 281 samples from 188 individuals who were administered mRNA vaccines, mainly Pfizer-BioNTech or Moderna vaccines. The control group consisted of 170 samples from 97 patients with COVID-19. The research group created a multiplexed surrogate virus neutralization test (plex-sVNT) that measures the ability of antibodies in serum to inhibit binding between ACE2 and seven trimeric S proteins of SARS-CoV-2 variants, including wild type, B.1.1.7(α), B.1.351(β), P.1(γ), B.1.617.2(δ), B.1.617.1(κ) and B.1.429(ε). The antibody neutralization ability was significantly decreased for all SARS-CoV-2 variants compared to the wild type in both infected and vaccinated individuals. At 5 months post-infection or vaccination, there was a noticeable decline in overall antibody neutralization activity, within both cohorts, with the rate of decrease being more significant for vaccinated individuals.[5]

Therapeutic strategies through the SARS-CoV-2 pandemic

Since the start of the SARS-CoV-2 pandemic, the focus of the scientific community has been on how to prevent mortality. Unfortunately, in many areas, healthcare systems underwent some degree of collapse. Therefore, attention was on the triage the new patients and defining the lines of therapy in either inpatient or outpatient settings. However, there are no specific criteria for admission due to COVID-19, as it varies according to the local resources and burden of disease. The National Institutes of Health recommends that those with an oxygen saturation of less than 94% in room air or with a respiratory rate exceeding 30 breaths/minute, PaO_2/FiO_2 less than 300 mmHg, should qualify for inpatient management.[16] The therapeutic agents for COVID-19 treatment generally involve mainly glucocorticoids, remdesivir, baricitinib, tocilizumab, and anticoagulation for inpatient treatment and sotrovimab, molnupiravir, remdesivir, bebtelovimab and convalescent plasma for outpatient treatment (Tables 1 and 2).

Monoclonal antibodies (mAb) are mass-produced antibodies obtained from a single B cell clone. They act upon the target antigen and deactivate and destroy it and have to ability to recruit other immune systems like the complement system. mAb is used in COVID-19 because of its ability to target the S protein of SARS-CoV-2.[35] mAb is a specific therapy utilized in the outpatient setting for patients with mild-to-moderate disease but significant risk factors that preclude progression to more severe disease. Although mAbs are expensive and only considered early in the disease course[17,18] with widely variable effects on the newly emerging strains (Table 1), they are the treatment of choice for high-risk populations, including immunocompromised patients such as those with cancer, transplant recipients or those taking immunosuppressant medications. In addition, patients with advanced cardiac, hepatic, or renal diseases are also considered for mAb treatment. Table 1 summarizes commonly used mAb agents, adverse reactions, and variant resistance.[17–21,24]

Therapies no longer used for SARS-CoV-2 treatment

Convalescent plasma

Convalescent plasma from individuals who have recovered from prior SARS-CoV-2 infection[36] was previously indicated in hospitalized patients and is currently not recommended as indicated by multiple randomized trials.[37,38]

Hydroxychloroquine

Hydroxychloroquine was initially used for the hypothesized in vitro antiviral effects against SARS-CoV-2 by blocking viral replication. However, due to low effective extracellular lung concentrations with regular doses, the in vitro antiviral property was not correlated with in vivo results. In addition, it has cardiotoxicity and increased risk of arrhythmias, such as torsade de points, especially when combined with the antibiotic azithromycin.[39,40]

Colchicine

Colchicine has anti-inflammatory effects by inhibiting tubule polymerization. It was previously studied in mild-to-moderate COVID-19 infection and was associated with a decreased hospitalization rate with no significant effect on mortality reduction.[41]

Table 1. Commonly used monoclonal antibody agents, adverse reactions, and variant resistance.

	Bamlanivimab-etesevimab[17,18]	Casirivimab-imdevimab[19–21]	Sotrovimab[22]	Bebtelovimab[23]	Tixagevimab-cilgavimab[24]
First FDA approval	November 9, 2020	November 21, 2020	May 26, 2021	February 2022	December 8, 2021
Target antigen	SARS-CoV-2 spike protein	Non-overlapping epitopes on the SARS-CoV-2 spike protein receptor-binding domain and block virus entry[22]	Conserved epitope on the spike protein receptor-binding domain of SARS-CoV-2	Spike protein of SARS-CoV-2	Non-overlapping epitopes of the spike protein receptor-binding domain of SARS-CoV-2, blocking attachment to the human ACE2 receptor
Adverse reactions	Infusion-related reaction	Ecchymoses, erythema at the injection site	Skin rash, diarrhoea, anaphylaxis, hypersensitivity reaction	Pruritus, skin rash, nausea, vomiting	Dizziness, fatigue, headache, anaphylaxis
Gamma variant resistance	Unlikely to be active (>511-fold decrease in susceptibility)	No change in susceptibility	No change in susceptibility	No change in susceptibility	
Omicron (sub-lineage BA.2) variant resistance		Up to 597-fold decreased susceptibility	Up to 50-fold decreased susceptibility	No change in susceptibility	Minimal change in susceptibility (5.4-fold decrease)
Omicron (sub-lineages BA.1 and BA.1.1) variant resistance	Inactive (>1013-fold decrease in susceptibility)	Inactive (>1013-fold decrease in susceptibility)	No change in susceptibility	No change in susceptibility	12- to 30-fold decrease in susceptibility for BA.1 and 176-fold decrease for BA.1.1

Due to varying susceptibilities of certain SARS-CoV-2 variants to different monoclonal antibody agents as shown above. The United States Food and Drug Administration routinely changes the Emergency Use Authorization of these agents based on the prevalence of the SARS-CoV-2 variants.

Enoxaparin

Enoxaparin was suggested to have anti-inflammatory effects by disrupting the hypoxia-inducible factor 1α pathway, mediating apoptosis and inflammation. However, there was no proven benefit between prophylactic *versus* therapeutic doses in patients without venous thromboembolism.[42–44]

COVID-19 vaccination

The development of various successful vaccines around the globe is striving to contain the exponential surge of COVID-19 cases. Since this pandemic started, the basic strategy to fight it was obtaining an effective, widely producible vaccination. SARS-CoV-2-specific RNA interference in conjunction with systemic delivery of compstatin was the promising strategy to improve local and systemic immune responses in patients with SARS-CoV-2.[45] The various available vaccines for COVID-19 are summarized in Table 3. Vaccine hesitancy, especially in the United States, is very prevalent and vaccine uptake rates, though improving significantly, are still not ideal. Vaccine hesitancy can be secondary to fear of adverse effects. Although by and large, most COVID-19 vaccines are well tolerated, there are some rare complications such as the incidence of myocarditis following vaccination with the mRNA COVID-19 vaccines[55–59] and an association with increased thrombocytopenia cases in an unusual prothrombotic state[60] and cerebral vein thrombotic events[61] following Janssen and AstraZeneca vaccines.

Goel et al.[62] examined antibody and memory B cell responses for 9–10 months in 61 individuals post mRNA vaccine administration (Pfizer BNT162b2 or Moderna mRNA-1273) following the initial two doses and 3 months after a third dose. Fortunately, Omicron-binding memory B cells were efficiently reactivated by a third dose with a significant increase in antibody titres.[62] Emphasizing the same results, Deshpande et al.[63] found that the neutralizing antibody responses were significantly elevated after a third dose of BBV152/Covaxin against

Table 2. Non-monoclonal antibody therapeutic tools for SARS-CoV-2.

	Mechanism of action	Indications	Dose	Limitations	Remarks
Steroids/ dexamethasone[25]	Broad immune inhibitory effects	Patients requiring oxygen supplementation	Dexamethasone 6 mg once daily, intravenous or oral, or an equivalent glucocorticoid dose, for 10 days	No benefits for patients not requiring supplemental oxygen	
Remdesivir[26,27]	Nucleotide analogue with antiviral activity	Hospitalized patients regardless of supplemental oxygen requirement	200 mg IV as loading, followed by 100 mg daily for 5–10 days	Not recommended in patients requiring mechanical ventilation and ECMO	No clear mortality benefits but reduce the course of hospitalization[26,27]
Baricitinib[28]	JAK (Janna kinase) inhibitor	In addition to remdesivir in hypoxic patients	4 mg once a day for 14 days		
Tocilizumab[29,30]	Blockade of IL-6 receptor with subsequent normalization of inflammatory markers, improved lung function and decreased mortality rate	Inpatient treatment of COVID-19 in patients treated with corticosteroids and supplemental oxygen, ventilatory support (invasive and non-invasive), or extracorporeal membrane oxygenation	8 mg/kg	Viral, bacterial and fungal infections, abnormal liver tests, hypercholesterolaemia, neutropenia, and anaphylaxis	Other agents acting on the IL-6 pathway: sarilumab (similar mechanism of action as tocilizumab) and siltuximab
Favipiravir[31]	RNA-dependent RNA polymerase inhibitor	Moderately ill patients with signs of respiratory distress and cytokine storm	Loading dose ~40 mg/kg for 10 days	Maculopapular rash, two with urticarial rash, and one with Stevens–Johnson syndrome[32]	Marketed in Japan (Avigan), China (Favilavir) and Russia (AVIFAVIR)
Nirmatrelvir-ritonavir (Paxlovid)[33]	Inhibitor of the SARS-CoV-2 main protease involved in viral replication; ritonavir inhibits hepatic metabolism by CYP3A and increases plasma concentrations	Symptomatic, unvaccinated outpatient individuals with a high risk of progression to severe disease to decrease the risk of hospitalization	300 mg nirmatrelvir and 100 mg ritonavir	Gastrointestinal side effects such as diarrhoea and distortion of the taste sensation, hypertension, musculoskeletal pain, hypersensitivity Resistance to Ritonavir if uncontrolled HIV	First FDA-approved oral antiviral for COVID-19
Molnupiravir[34]	Nucleoside analogue	Within 5 days after symptom onset in non-hospitalized, unvaccinated adults with mild-to-moderate COVID-19	800 mg twice daily for 5 days	Diarrhoea, bacterial pneumonia	Second oral antiviral authorized by FDA after paxlovid

Table 3. Available vaccinations for COVID-19.

	Mechanism of action	Dose	Side effects
Moderna (mRNA-1273)[46]	mRNA vaccine delivered in lipid nanoparticles to express the spike protein	Two divided doses of 100 mcg each 28 days apart, intramuscularly Booster of 50 mcg 5 months after primary series	Myalgia, fatigue, injection site pain, fevers and chills; myocarditis, pericarditis and myopericarditis have been reported
Pfizer (BNT 162b2)[46]	mRNA vaccine in lipid nanoparticle	Two divided doses of 30 mcg, 21 days apart; booster of 30 mcg 5 months after primary series	
Janssen/Johnson and Johnson (Ad26.COV2.S)[47]	Replication of incompetent adenovirus vector vaccine	0.5 mL single-dose vaccine Booster: available booster, which is also 0.5 mL given 2 months after the primary	Headache, fatigue and injection site pain, tachycardia, dizziness and syncope, thrombosis with thrombocytopenia, and Guillain-Barre syndrome
AztraZeneca (ChAdOx1 nCoV-19/ AZD1222)[48]	Replication of incompetent virus vector vaccine	Two divided doses, intramuscularly, 4–12 weeks apart; unfortunately, there is no booster dose available at this moment	Fatigue, headache, fever, thrombosis with thrombocytopenia
Covaxin (BBV 152)[49]	Inactivated virus	Two doses 29 days apart	Injection site pain, fatigue, headache and muscle aches
Novovax (NVX-cov2373)[50]	Recombinant protein nanoparticle vaccine	Two doses (0.5 mL), intramuscularly, at an interval of 3–4 weeks	Headache, fever, fatigue, muscle aches, nausea, pain, irritation, redness and injection site swelling
Sinovac[51]	Inactivated vaccine	Two doses 28 days apart	Nausea and a rare neurological disorder
Sinopharm (WIV04 and HB02)[52]	Inactivated vaccine	Two doses 28 days apart	Injection site pain, fatigue and headache
Sputnik V[53]	Replication incompetent adenovirus vector vaccine (uses two separate vectors) developed by Gamaleya institute in Russia	First dose with the adenovirus 26 vector dose, second dose with adenovirus 5 vector 21 days to 3 months after the first dose	Fatigue (70%), headache (64%), muscle pain (61%), joint pain (46%), chills, nausea and vomiting
Cansino biologics Ad5-based COVID-19 vaccine[54]	Replication of incompetent adenovirus vector	Single intramuscular dose	Redness, fatigue, fever, nausea, headaches and muscle pains

the Delta (17-fold), Beta (15-fold), and Omicron (19-fold) variants compared with the two-dose protocol.[63] To assess the immune response in patients at high risk, Šušol et al.[64] studied the effect of the third mRNA Pfizer vaccine in 80 patients with haematological malignancy with poor serological response to the two-dose protocol. They found that the third dose succeeded in inducing the desirable serological response.[64] Another vulnerable group to severe COVID-19 infections are the elderly living in nursing homes. Jeulin et al.[65] found that the third dose induced a more pronounced antibody titre than the second dose, especially in those without prior COVID-19 infection exposure. This titre is believed to provide prolonged protection against severe COVID-19 in these patients.[65] In contrast to the previous results, Goel et al.[62] found that the antibody titres before the third booster dose were inversely correlated with the subsequent increase in antibodies. In other words, high levels of circulating antibodies may lessen the expected additional protection if boostered within a short interval in the general population.[62] This finding is not typical for the immunocompromised population. In May 2022, CDC announced the recommendations of four doses of mRNA COVID-19 vaccine for people over 12 years old with who are moderately or severely immunocompromised. The four doses include an initial three doses of Pfizer-BioNTech or Moderna vaccines, followed by one booster of Pfizer-BioNTech or Moderna COVID-19 vaccine (fourth

dose). For those between the ages of 12 and 17 years, only Pfizer-BioNTech COVID-19 vaccine has been studied.[66]

Schiffner et al.[67] enrolled 412 adults, mostly with mild or moderate disease, to evaluate their acquired B and T cell immune responses. Both circulating IgG antibody levels and IFNγ decreased by about half within 300 days after acute SARS-CoV-2 infection. In other words, immunological reactions after natural infection can be sustained in most patients for at least 10 months.[67] Poorer SARS-CoV-2 antibody response was noticed in those with 1-year duration long COVID syndrome.[68]

Long COVID syndrome

The exact pathophysiology of long COVID syndrome is still unknown. Hypotheses include possible pulmonary or neurological tissue damage with or without tissue inflammation from direct viral injury or immune-mediated inflammation. Long COVID is more prevalent in female gender and patients psychiatric conditions. Variable percentages of patients recovered from COVID-19 reported fatigue, cognitive dysfunction, headache, breathing difficulties, chest pain, and smell and taste dysfunctions. The clinical severity may be correlated with inflammatory markers such as CRP, D-dimer and lymphocyte count.[69] Other suggested mechanisms are diffuse endothelial damage and microthrombi formation.[70] Asadi-Pooya et al.[71] studied 2696 patients with confirmed COVID-19 3 months after the acute illness. They found that 62.3% of patients reported long COVID syndrome, with 7.2% reporting brain fog. There were significant associations between brain fog and respiratory symptoms at the onset of disease and the need for intensive care unit level during the initial illness.

Conclusion

The current evidence suggests that vaccines are effective against SARS-CoV-2 variants. Apart from the influenza virus, the variants of which have been known to escape monoclonal antibodies, no virus has been shown to entirely evade the immune response generated by vaccines. The influenza virus has a high mutation rate and needs a new vaccine developed yearly.[72] There are limited data regarding vaccine efficacy in high-risk groups such as patients with cancer, with a lack of clinical evidence for the guidance of the vaccination protocols in such patients. High-risk groups, including those with obesity, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus, and cardiovascular diseases,[73,74] for whom vaccination protection may be attenuated, now carry a tremendous burden of risk amongst the population. Multiple potential future scenarios exist, ranging from complete protection from COVID-19 for patients at high risk via herd immunity to viral evolution for vaccine resistance and increased virulence. As the pandemic progresses, protecting those at high risk would avoid complications and may enable a return to normal for the majority.[75] Continued genomic surveillance is needed for early detection of any variants that may escape neutralizing antibodies so that vaccines can be updated accordingly. To win the battle against COVID-19, we have to improve the sequencing capabilities, convalescent plasma and other factors to study how viruses respond to antibodies. Finally, it is imperative to follow strict social distancing protocols to prevent the transmission of the virus whilst the vaccines are administered.[72]

Contributions: TJV, MRG and SC conceptualized this manuscript. SC is the principal author. All coauthors contributed to the initial writing of the manuscript. MS helped in preparation of tables and final round of edits. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2023/01/dic.2022-7-2-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/covid-19-therapy-and-vaccination-a-clinical-narrative-review

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Provenance: Invited; externally peer reviewed.

Submitted: 4 July 2022; **Accepted:** 5 January 2023; **Published:** 7 February 2023.

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BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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References

1. Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 Vaccine effectiveness in a high-risk national population in a real-world setting. *Ann Intern Med*. 2021;174(10):1404–1408. https://doi.org/10.7326/m21-1577
2. Araf Y, Faruqui NA, Anwar S, Hosen MJ. SARS-CoV-2: a new dimension to our understanding of coronaviruses. *Int Microbiol*. 2021;24(1):19–24. https://doi.org/10.1007/s10123-020-00152-y
3. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021;19(3):1. https://doi.org/10.1038/s41579-020-00459-7
4. Saban M, Myers V, Peretz G, Avni S, Wilf-Miron R. COVID-19 morbidity in an ethnic minority: changes during the first year of the pandemic. *Public Health*. 2021;198:238–244. https://doi.org/10.1016/j.puhe.2021.07.018
5. Wang CS, Gao Y, Kang K, et al. Standardization of critical care management of non-critically ill patients with COVID-19. *World J Clin Cases*. 2021;9(12):2696–2702. https://doi.org/10.12998/wjcc.v9.i12.2696
6. Benedetti C, Waldman M, Zaza G, Riella LV, Cravedi P. COVID-19 and the kidneys: an update. *Front Med*. 2020;7:423. https://doi.org/10.3389/fmed.2020.00423
7. Gagliardi I, Patella G, Michael A, Serra R, Provenzano M, Andreucci M. COVID-19 and the kidney: from epidemiology to clinical practice. *J Clin Med*. 2020;9(8):2506. https://doi.org/10.3390/jcm9082506
8. Rana R, Tripathi A, Kumar N, Ganguly NK. A comprehensive overview on COVID-19: future perspectives. *Front Cell Infect Microbiol*. 2021;11:744903. https://doi.org/10.3389/fcimb.2021.744903
9. Liu P, Jiang JZ, Wan XF, et al. Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)? *PLoS Pathog*. 2020;16(5):e1008421. https://doi.org/10.1371/journal.ppat.1008421
10. Kadam SB, Sukhramani GS, Bishnoi P, Pable AA, Barvkar VT. SARS-CoV-2, the pandemic coronavirus: molecular and structural insights. *J Basic Microbiol*. 2021;61(3):180. https://doi.org/10.1002/jobm.202000537
11. Papanikolaou V, Chrysovergis A, Ragos V, et al. From delta to Omicron: S1-RBD/S2 mutation/deletion equilibrium in SARS-CoV-2 defined variants. *Gene*. 2022;814:146134. https://doi.org/10.1016/j.gene.2021.146134
12. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. 2021;596(7871):276–280. https://doi.org/10.1038/s41586-021-03777-9
13. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385(7):585–594. https://doi.org/10.1056/nejmoa2108891
14. Garcia-Beltran WF, St. Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185(3):P457–466.E4. https://doi.org/10.1016/j.cell.2021.12.033

15. Fantini J, Yahi N, Colson P, Chahinian H, La Scola B, Raoult D. The puzzling mutational landscape of the SARS-2-variant Omicron. *J Med Virol*. 2022;94(5):2019–2025. https://doi.org/10.1002/jmv.27577
16. Management. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/management/. Accessed June 27, 2022.
17. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med*. 2021;385(15):1382–1392. https://doi.org/10.1056/nejmoa2102685
18. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021;325(7):632–644. https://doi.org/10.1001/jama.2021.0202
19. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. *N Engl J Med*. 2021;385(23):e81. https://doi.org/10.1056/nejmoa2108163
20. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238–251. https://doi.org/10.1056/nejmoa2035002
21. Fact sheet for health care providers: highlights of Emergency Use Authorization (EUA) for REGEN-COV ® (casirivimab and imdevimab). Published online 2022. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Accessed August 28, 2022.
22. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: a randomized clinical trial. *JAMA*. 2022;327(5):432–441. https://doi.org/10.1001/jama.2021.24939
23. Fact sheet for healthcare providers: highlights of Emergency Use Authorization (EUA) for bebtelovimab. These highlights of the EUA do not include all the information needed to use BEBTELOVIMAB under the EUA. See the full fact sheet for healthcare providers for BEBTELOVIMAB. BEBTELOVIMAB injection for intravenous use Original. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Accessed August 28, 2022.
24. Major changes recent. Fact sheet for health care providers: highlights of Emergency Use Authorization (EUA) for EVUSHELD™ (tixagevimab co-packaged with cilgavimab). These highlights of the EUA do not include all the information needed to use EVUSHELD™ under the EUA. See the full fact sheet for healthcare providers for EVUSHELD. EVUSHELD (tixagevimab) injection; (cilgavimab) injection, co-packaged for intramuscular use Original EUA. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Accessed November 1, 2022.
25. Bhimraj A, Morgan RL, Hirsch Shumaker A, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. Last updated November 21, 2022. https://www.idsociety.org/COVID19guidelines. Accessed November 12, 2022.
26. Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020;370:m2980. https://doi.org/10.1136/bmj.m2980
27. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569–1578. https://doi.org/10.1016/s0140-6736(20)31022-9
28. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407–1418. https://doi.org/10.1016/s2213-2600(21)00331-3
29. Tleyjeh IM, Kashour Z, Damlaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(2):215–227. https://doi.org/10.1016/j.cmi.2020.10.036
30. Coronavirus (COVID-19) update: FDA authorizes drug for treatment of COVID-19. FDA. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19. Accessed March 20, 2022.
31. Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate Coronavirus disease 2019 (COVID-19): interim results of a phase II/III multicenter randomized clinical trial. *Clin Infect Dis*. 2021;73(3):531–534. https://doi.org/10.1093/cid/ciaa1176
32. Punyaratabandhu P, Vanitchpongphan S. Favipiravir-induced cutaneous adverse reactions in patients infected with COVID-19. *Clin Exp Dermatol*. 2022;47(3):573–577. https://doi.org/10.1111/ced.14953
33. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386:1397–1408. https://doi.org/10.1056/nejmoa2118542
34. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509–520. https://doi.org/10.1056/nejmoa2116044
35. Zhao A, Tohidkia MR, Siegel DL, Coukos G, Omidi Y. Phage antibody display libraries: a powerful antibody discovery platform for immunotherapy. *Crit Rev Biotechnol*. 2016;36(2):276–289. https://doi.org/10.3109/07388551.2014.958978

36. Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol*. 2021;7(8):1167–1175. https://doi.org/10.1001/jamaoncol.2021.1799
37. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. 2021;384(7):619–629. https://doi.org/10.1056/nejmoa2031304
38. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020;371:m3939. https://doi.org/10.1136/bmj.m3939
39. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(1):19–27. https://doi.org/10.1016/j.cmi.2020.08.022
40. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383(21):2041–2052. https://doi.org/10.1056/nejmoa2019014
41. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924–932. https://doi.org/10.1016/s2213-2600(21)00222-8
42. Billett HH, Reyes-Gil M, Szymanski J, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality. *Thromb Haemost*. 2020;120(12):1691–1699. https://doi.org/10.1055/s-0040-1720978
43. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv*. 2021;5(3):872–888. https://doi.org/10.1182/bloodadvances.2020003763
44. Hanif A, Khan S, Mantri N, et al. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. *Ann Hematol*. 2020;99(10):2323–2328. https://doi.org/10.1007/s00277-020-04216-x
45. Naqvi RA, Shukla D, Naqvi AR. SARS-CoV-2 targeting by RNAi and host complement inhibition: a two-pronged subterfuge for COVID-19 treatment. *Immun Inflamm Dis*. 2022;10(1):22–25. https://doi.org/10.1002/iid3.549
46. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. *N Engl J Med*. 2021;385(15):1355–1371. https://doi.org/10.1056/nejmoa2110362
47. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187–2201. https://doi.org/10.1056/nejmoa2101544
48. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881–891. https://doi.org/10.1016/s0140-6736(21)00432-3
49. Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis*. 2021;21(5):637–646. https://doi.org/10.1016/s1473-3099(20)30942-7
50. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. *N Engl J Med*. 2022;386(6):531–543. https://doi.org/10.1056/nejmoa2116185
51. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213–222. https://doi.org/10.1016/s0140-6736(21)01429-x
52. Xia S, Duan K, Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *JAMA*. 2020;324(10):951–960. https://doi.org/10.1001/jama.2020.15543
53. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet*. 2020;396(10255):887–897. https://doi.org/10.1016/s0140-6736(20)31866-3
54. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2020;396(10249):479–488. https://doi.org/10.1016/s0140-6736(20)31605-6
55. Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA*. 2022;327(4):331–340. https://doi.org/10.1001/jama.2021.24110
56. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol*. 2021;6(10):1202–1206. https://doi.org/10.1001/jamacardio.2021.2833
57. Muthukumar A, Narasimhan M, Li QZ, et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. *Circulation*. 2021;144(6):487–498. https://doi.org/10.1161/circulationaha.121.056038

58. Park J, Brekke DR, Bratincsak A. Self-limited myocarditis presenting with chest pain and ST segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine. *Cardiol Young*. 2022;32(1):146–149. https://doi.org/10.1017/s1047951121002547
59. Kim RJ, Kim HW, Jenista ER, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. *JAMA Cardiol*. 2021;6(10):1196–1201. https://doi.org/10.1001/jamacardio.2021.2828
60. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(22):2124–2130. https://doi.org/10.1056/nejmoa2104882
61. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. *J Neurol Sci*. 2021;428:117607. https://doi.org/10.1016/j.jns.2021.117607
62. Goel RR, Painter MM, Lundgreen KA, et al. Efficient recall of Omicron-reactive B cell memory after a third dose of SARS-CoV-2 mRNA vaccine. *Cell*. 2022;185(11):P1875–1887.E8. https://doi.org/10.1016/j.cell.2022.04.009
63. Deshpande GR, Yadav PD, Abraham P, et al. Booster dose of the inactivated COVID-19 vaccine BBV152 (Covaxin) enhances the neutralizing antibody response against alpha, Beta, Delta and omicron variants of concern. *J Travel Med*. 2022;29(3):taac039. https://doi.org/10.1093/jtm/taac039
64. Šušol O, Hájková B, Zelená H, Hájek R. Third dose of COVID-19 vaccine restores immune response in patients with haematological malignancies after loss of protective antibody titres. *Br J Haematol*. 2022;197(3):302–305. https://doi.org/10.1111/bjh.18073
65. Jeulin H, Labat C, Duarte K, et al. Anti-spike IgG antibody kinetics following the second and third doses of BNT162b2 vaccine in nursing home residents. *J Am Geriatr Soc*. 2022;70(9):2552–2560. https://doi.org/10.1111/jgs.17837
66. CDC. COVID-19 vaccines for people who are moderately or severely immunocompromised. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. Accessed May 22, 2022.
67. Schiffner J, Backhaus I, Rimmele J, et al. Long-term course of humoral and cellular immune responses in outpatients after SARS-CoV-2 infection. *Front Public Health* 2021;9:732787. https://doi.org/10.3389/fpubh.2021.732787
68. García-Abellán J, Fernández M, Padilla S, et al. Immunologic phenotype of patients with long-COVID syndrome of 1-year duration. *Front Immunol*. 2022;13:920627. https://doi.org/10.3389/fimmu.2022.920627
69. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis*. 2021;53(10):737–754. https://doi.org/10.1080/23744235.2021.1924397
70. Piazza M, Di Cicco M, Pecoraro L, Ghezzi M, Peroni D, Comberiati P. Long COVID-19 in children: from the pathogenesis to the biologically plausible roots of the syndrome. *Biomolecules*. 2022;12(4):556. https://doi.org/10.3390/biom12040556
71. Asadi-Pooya AA, Akbari A, Emami A, et al. Long COVID syndrome-associated brain fog. *J Med Virol*. 2022;94(3):979–984. https://doi.org/10.1002/jmv.27404
72. Jogalekar MP, Veerabathini A, Gangadaran P. SARS-CoV-2 variants: a double-edged sword? *Exp Biol Med*. 2021;246(15):1721–1726. https://doi.org/10.1177/15353702211014146
73. Fukushima K, Yamada Y, Fujiwara S, et al. Development of a risk prediction score to identify high-risk groups for the critical Coronavirus disease 2019 (COVID-19) in Japan. *Jpn J Infect Dis*. 2021;74(4):344–351. https://doi.org/10.7883/yoken.jjid.2020.789
74. Holstiege J, Akmatov MK, Kohring C, et al. Patients at high risk for a severe clinical course of COVID-19 – small-area data in support of vaccination and other population-based interventions in Germany. *BMC Public Health*. 2021;21(1):1769. https://doi.org/10.1186/s12889-021-11735-3
75. Little M, Fittall M, McKenzie H, Tilby M, Tripathy A, Lee LYW. As COVID-19 cases surge despite mass vaccination, it's time to focus on the vulnerable. *Ecancermedicalscience*. 2021;15:ed117. https://doi.org/10.3332/ecancer.2021.ed117