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Review Paper

From bench to bedside: potential of translational research in COVID-19 and beyond

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) have been around for more than 3 years now. However, due to constant viral evolution, novel variants are emerging, leaving old treatment protocols redundant. As treatment options dwindle, infection rates continue to rise and seasonal infection surges become progressively common across the world, rapid solutions are required. With genomic and proteomic methods generating enormous amounts of data to expand our understanding of SARS-CoV-2 biology, there is an urgent requirement for the development of novel therapeutic methods that can allow translational research to flourish. In this review, we highlight the current state of COVID-19 in the world and the effects of post-infection sequelae. We present the contribution of translational research in COVID-19, with various current and novel therapeutic approaches, including antivirals, monoclonal antibodies and vaccines, as well as alternate treatment methods such as immunomodulators, currently being studied and reiterate the importance of translational research in the development of various strategies to contain COVID-19.

Nityendra Shukla is involved in developing computational workflows and approaches for improved genomic surveillance of SARS-CoV-2. He also works on the analysis of microbial and metagenomic sequencing data.
Uzma Shamim is interested in expanding the use of genomics to investigate the dynamics of host–pathogen interactions in infectious diseases.
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Jitendra Narayan is interested in evolutionary mechanisms, such as chromosomal breakage and horizontal gene transfer, and specializes in the development of computational approaches to assist in the understanding of viral and eukaryotic evolution.
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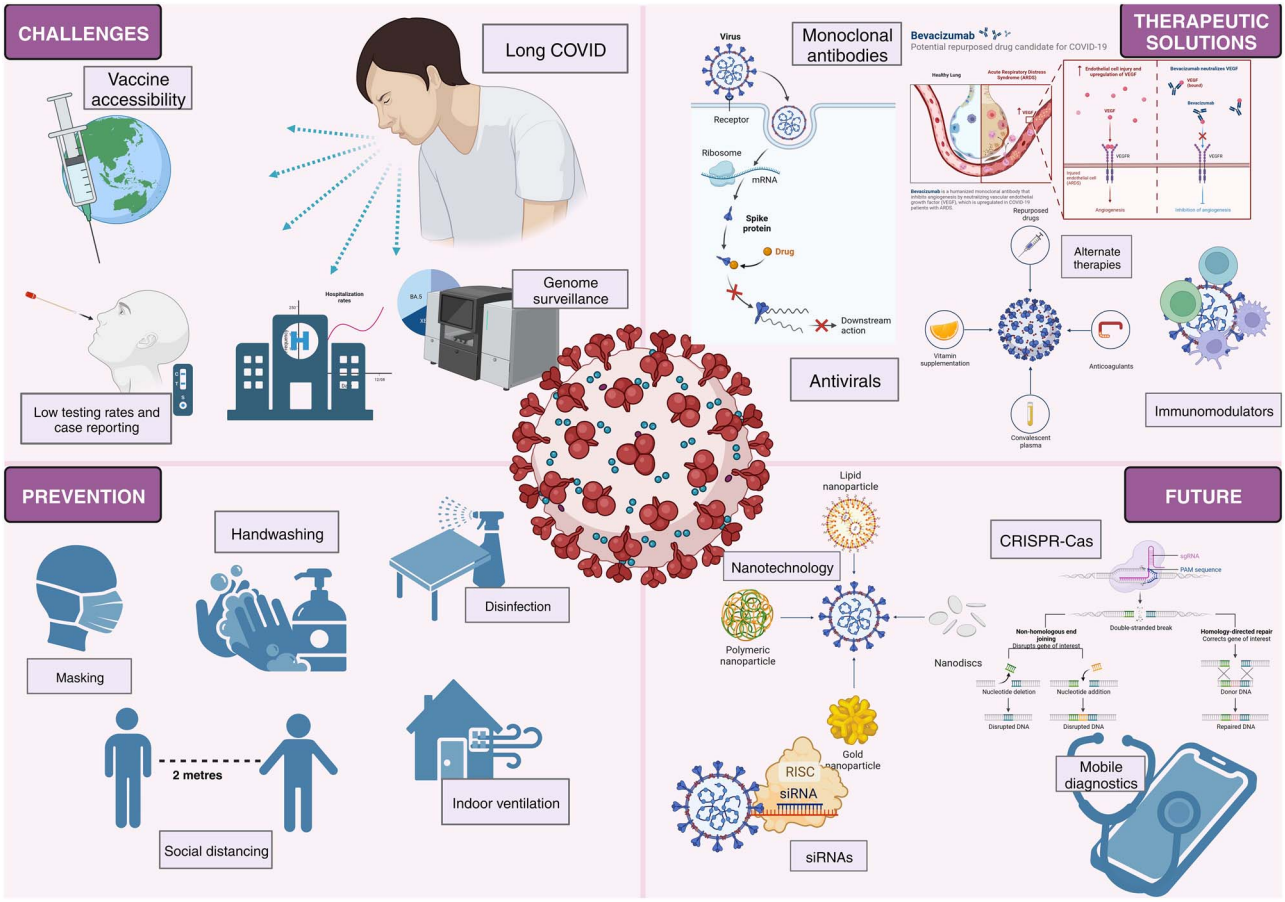
Graphical Abstract



Summarizing the challenges, therapeutic and preventive approaches with translational strategies to contain COVID-19.

Keywords: translational research; COVID-19; SARS-CoV-2; vaccine equity; genomic surveillance; therapeutics

INTRODUCTION

The coronavirus disease 2019 (COVID-19), first discovered in Wuhan, China in December 2019, spread rapidly throughout the world resulting in the first pandemic of the twenty-first century, drawing parallels to the 1918 Spanish flu pandemic [1]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. As of 27 January 2023, 752 million cases and 6.8 million deaths worldwide have been reported [3]. A significant number of resources were deployed against COVID-19 to limit its spread, including mitigation techniques such as face mask mandates, social distancing and lockdowns, as well as research into the biology and pathogenesis of SARS-CoV-2 in order to develop therapeutics to treat clinical complications such as lung injuries, cytokine storm syndrome (CSS), thrombosis, strokes and neurological complications to reduce mortality [4].

Moreover, long COVID or post-acute sequelae of COVID-19 has been a concerning issue and presents as a major complication, due to its broad range of symptoms, often severe and multi-systemic in nature, and SARS-CoV-2 infection persistence for months, which usually does not resolve. Due to a large number of undocumented cases and a lack of awareness about the condition, the number of long COVID patients is probably much higher than reported [5]. An online survey conducted across COVID-19 support groups and social media over a period of 3 months discovered that post-COVID symptoms persisted for more than 6 months and the time to recovery exceeded 35 weeks [6].

The role of translational research has been instrumental in COVID-19 mitigation efforts, yet there is still a lack of novel diagnostic and therapeutic options. Immunocompromised individuals and people with comorbidities remain at high risk of severe complications from the infection. In addition, the rapidly evolving nature of the virus makes existing treatment options, such as antivirals and monoclonal antibodies (mABs), ineffective, especially against emerging Omicron sub-lineages gaining resistance to most mABs [7]. Thus, 'translating' our understanding of disease mechanisms and other aspects of biology gained through basic science into functional methods in clinical settings is the primary goal of translational research. Analysis and interpretation of various kinds of data gained through computational and experimental techniques need to be shared between basic science researchers and clinicians. Observations gained from hospital settings about disease etiology and progression can drive basic science research and result in potential therapeutics or strategies that can be communicated to clinicians for the next stage of clinical testing.

The success of translational research in the ongoing pandemic can be gaged by the development of various types of vaccines, including the first-ever mRNA vaccines against

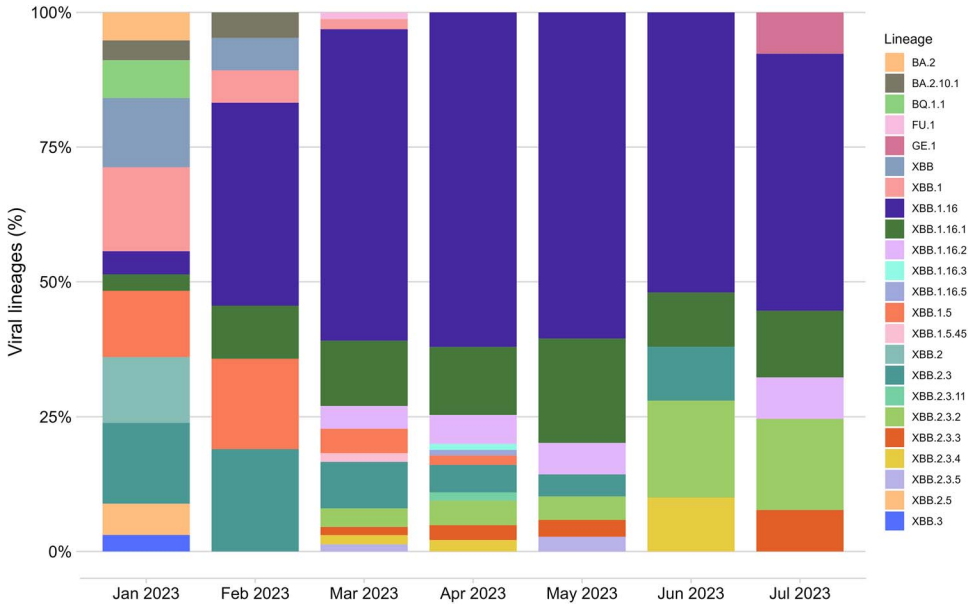


Figure 1: Distribution of various SARS-CoV-2 variants in India. It displays emerging variants gaining dominance in the local population, with XBB.1.16 being responsible for the spring 2023 wave in India.

COVID-19 in record time [8]. Nevertheless, high-quality preclinical and translational studies on COVID-19 can further help to elucidate the mechanisms of infection and reinfection by evolving variants, as well as therapeutic interventions that might benefit acute manifestations and long-term COVID-19 complications. In this review, we provide an overview of the current challenges hindering translational research efforts in the present global COVID-19 scenario. We also highlight how translational research has augmented medications and therapeutics during the pandemic crisis, as well as how it can be maneuvered to maximize its benefits.

NAVIGATING THE GLOBAL LANDSCAPE: UNDERSTANDING CURRENT REALITIES AND OVERCOMING GLOBAL CHALLENGES

After 2 years of rigorous mitigation efforts in combating the COVID-19 pandemic, it seems the majority of governments around the world have considered it to be over with countries scaling back heavily on testing and genome sequencing [9] or scrapping it entirely [10]. The reality, however, is different as newer, fitter variants are emerging consistently, fighting for dominance and causing seasonal waves (Figure 1) [11]. The narrative across the West continues to be that we have to 'live with the virus' [12–14] or that it will 'evolve to become like the common cold' [15–17]. Though SARS-CoV-2 testing has been practically abandoned [18] and genome surveillance rates remain low, the most recent EG.5 variant has caused a global rise in cases and hospitalizations in several countries, especially high-income countries (HICs) (Figure 2) [19].

Although case numbers have decreased drastically since the peak of the pandemic, SARS-CoV-2 reinfection is still a cause for concern with healthcare workers (HCWs) at the highest risk. Reinfection rates among HCWs have been highest since the introduction of the Omicron variant, with Guedes *et al.* [21] reporting a reinfection rate of 0.8% before Omicron and 4.3% after Omicron. Similarly, reinfection rates across continents varied widely with America, Asia and Europe reporting reinfection rates at 1.08, 0.77 and 0.63%, respectively [22]. In addition, individuals with one or more reinfections exhibited a higher risk of hospitalization and all-cause mortality, by 3.32 and 2.17 times, respectively [23]. Comparative analyses against control revealed the risk of damage to organ systems and development of comorbidities displayed direct correlation with the number of reinfections in both acute and post-acute phases. The cumulative risk of developing at least one sequela increases by 2.10 times after the first reinfection and continues to increase as the number of reinfections increases. The risks were present in all individuals, regardless of their vaccination status, therefore making public health mitigation efforts all the more important to prevent reinfections [23].

SARS-CoV-2 infection rates in children and adolescents have also been high, with infections and hospitalizations surging and vaccination rates low [24]. As of January 2023, 15.2 million COVID-19 cases in children have been reported in the United States alone, with children comprising 18.1% of the total caseload [24]. Globally, confirmed cases in children of ages less than 5 years and 5–14 years stand at 7.9 million and 32.1 million, respectively [3]. A total of 75 529 children aged 5–17 were infected with COVID-19 during the span of a year between March 2020 and February 2021. Of which, 1734 children were symptomatic but interestingly, the duration of illness was much lower in children (6 days) than in adults (11 days) [25]. While the rate of death in children was low (1.2%), 75% of the deaths occurred in neurodisabled and immunocompromised individuals [26]. Similarly, in China, most of the affected children aged between 2 and 13 were less likely to develop severe symptoms, but young children, especially infants, were particularly at risk of infection. Importantly, in an inter-related way, the pandemic has also affected access of routine immunization protocols in developing countries, exposing children to infections other than SARS-CoV-2 [27].

Mitigation and vaccination efforts need to be strengthened in reducing infection rates so that serious complications such as long COVID or multisystem inflammatory syndrome in children (MIS-C) can be prevented, especially in children with high-risk

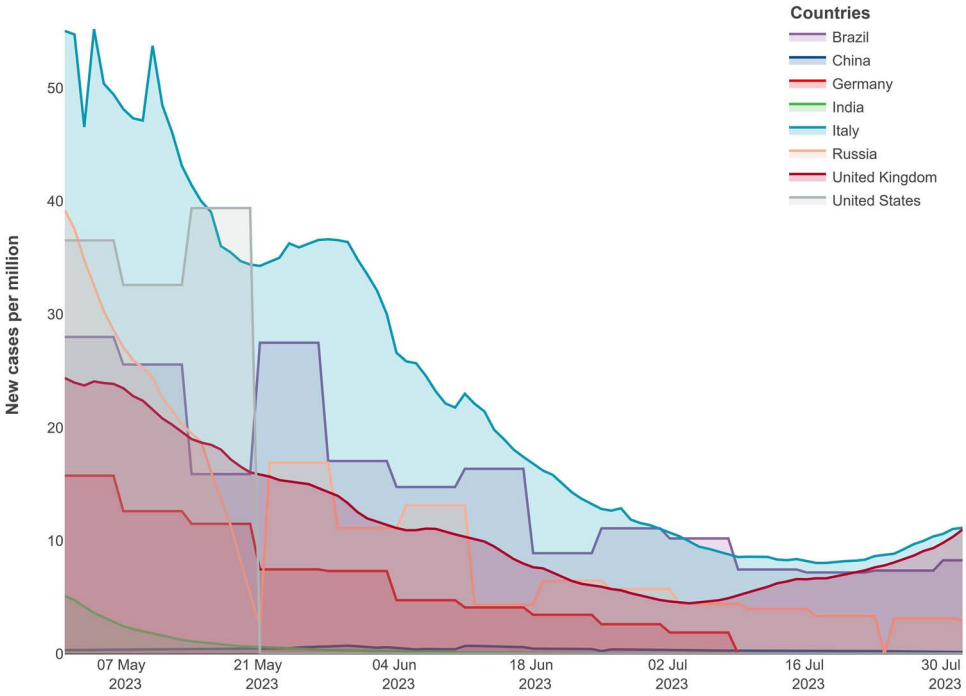


Figure 2: Cases per million over the past 2 months in countries with different economies as of 30 July 2023 [20].

conditions such as lung disease, neurologic and cardiovascular disorders [28], as well as those belonging to ethnic and racial communities, since a disproportionately high number of children that were infected throughout the pandemic belonged to minority groups [29–31] as well as higher rates of hospitalization [32, 33] and MIS-C [30, 34]. Vaccination rates in children have also been low due to vaccine hesitancy and slow implementation, with children belonging to low-income and lower-middle-income countries being the most affected [35].

However, health disparities among communities were not limited to children, with both racial and socioeconomic status affecting access to quality healthcare. This led to increased mortality rates among minorities or individuals living in poverty or in the lower-income bracket [36, 37], highlighting vaccine inequity as a hovering global issue [38]. The vaccine inequity has been extremely evident on the international level, with HICs achieving high vaccination rates as compared to low- and middle-income countries (LMICs) (Figure 3) [39]. Worldwide vaccine distribution is controlled by pharmaceutical companies, with the primary model of vaccine acquisition being through financial competition, resulting in HICs having access and, in some cases, leading to vaccine wastage [39–41] due to vaccine hoarding [42].

The consequences of vaccine inequity impacted the whole world, with it being the major driving cause of new emerging variants as seen previously with the Omicron variant [43]. The COVID-19 Vaccines Global Access (COVAX) initiative has proved to be not as effective as previously thought, with an acute imbalance of vaccine distribution worldwide. The Agreement of Trade-Related Aspects of Intellectual Property Rights (TRIPS) waiver, first proposed by India and South Africa in October 2020 [44], had support from majority of the WTO countries but was opposed by some major HIC members. Relinquishing intellectual property (IP) rights is the first step toward global equitable vaccine access, with the goal being to create a collaborative, centralized, global technology transfer hub.

THE LINGERING IMPACT: UNDERSTANDING LONG-TERM COVID-19 SYMPTOMS AND EFFECTS

Long COVID or post-acute sequelae of COVID-19 remains a challenge, as the number of cases seems to be increasing. There is a great diversity of symptoms, some debilitating, that greatly affect quality of life, as it involves multiple organ systems [45]. The number of long COVID patients is conservatively estimated to be about 10% of all the SARS-CoV-2 infections, bringing the number to around 65 million globally [45]. The real number, in all probability, is a lot higher due to undocumented cases. Long COVID manifested most in patients who displayed mild COVID-19 symptoms and did not require hospitalization, with most cases being between the ages of 36 and 50 [46]. Long COVID patients suffer from an extensive range of symptoms across a wide range of organ systems, with hundreds of biomedical findings. Cognitive (brain fog, poor attention span, difficulty thinking), musculoskeletal (tightness of chest, muscle aches), pulmonary (shortness of breath, dry cough), cardiovascular (palpitations, tachycardia) and systemic (fatigue, post-exertional malaise) symptoms were the most prevalent, experienced by greater than 60% individuals who participated in a survey [6]. Furthermore, post-infection follow-up in symptomatic patients at 6, 12 and 18 months revealed that almost half of the group reported incomplete or no recovery, with cardiovascular symptoms such as breathlessness, palpitations and chest pain being most prominent, and an overall decreased quality of life [47]. Sleep issues and mental health disorders such as depression and anxiety have also been reported [48, 49]. In many cases, serious disorders such as type 2 diabetes [50], dysautonomia [51] and myalgic encephalomyelitis/chronic fatigue syndrome [52, 53] have been chronicled, resulting in disability [6, 54] and has been cited as a major cause of labor shortage in the United States [55, 56]. Similarly, daily wage migrant workers in countries like India and China were affected the most from the pandemic since their daily income was terminated due to nationwide lockdowns with no safety net to support them,

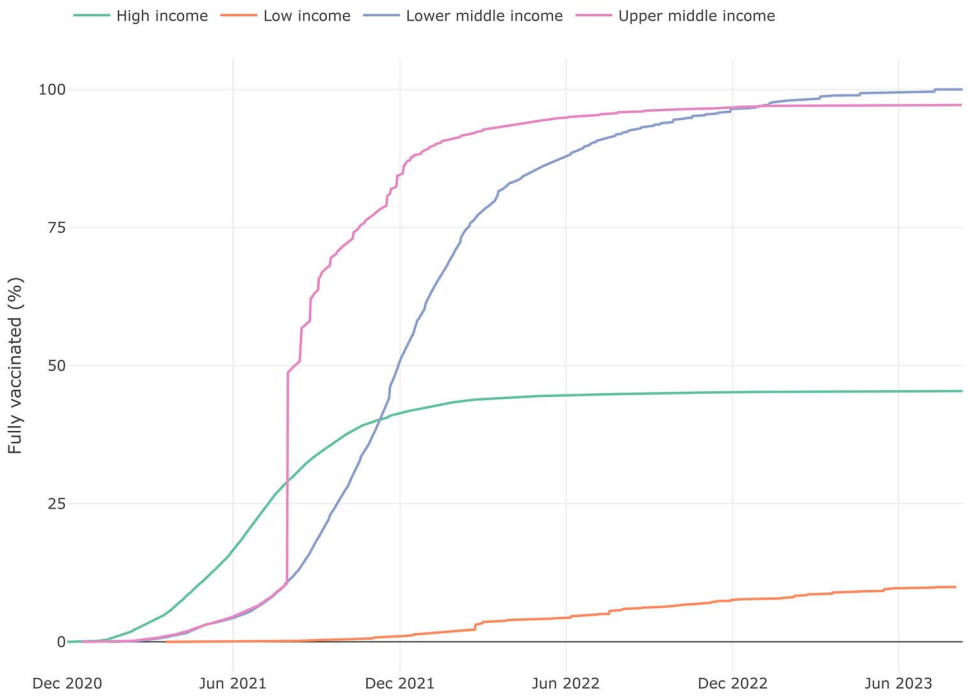


Figure 3: Line plot of fully vaccinated (two doses) populations per 100 people in differing economies as of 30 August 2023. Upper-middle-income countries have the highest vaccination rates, with vaccination rates in LMICs increasing since mid-2021 and low-income countries rising steadily since 2022 yet remains low [20].

causing severe economic and mental strain [57]. The Americans with Disabilities Act formally recognized long COVID as a disability in July 2021 [58] and in the UK [59]. No effective treatments currently exist to treat long COVID.

Multiple causes of long COVID have been hypothesized, with prolonged release of immune and inflammatory factors being one of the major causes driving its progression [58]. Ortelli *et al.* [60] observed a hyper-inflammatory state, characterized by high levels of C-reactive protein (CRP) and interleukin-6 (IL-6) levels during the acute infection phase in COVID-19 patients suffering from fatigue and neurological complications post-infection in 12 patients. Klein and colleagues reported high number of non-conventional monocytes as well as higher absolute counts of double-negative B cells in long COVID patients. Other immune markers such as CD4 T cells, contributing to increased levels of inflammatory markers IL-4/IL-6, were increased and dendritic cells DC1 and central-memory CD4 T cells were decreased [61]. Prolonged viral reservoirs post-infection [62] with neuroinvasive and neurotrophic potential of SARS-CoV-2 have been recorded [63, 64] in human and mice studies. Host immune system dysregulation has been conspicuous in COVID-19 [65, 66] and has been conjectured to play some role in long COVID [62], with activation of some dormant pathogens such as Herpesviruses or *Toxoplasma* also observed [62] which may or not play an additional role in immune system dysregulation.

Long COVID also affects children of all ages and, due to testing issues and lack of research, are harder to diagnose. Studies have ascertained that certain groups are more prone to severe complications, such as obesity, neurologic comorbidities, congenital disorders and pulmonary disease, among others. COVID-19 in children and adolescents has been of particular concern and cases have been steadily rising since the pandemic began due to reduced vigilance in preventing infections. A Schools Infection Survey by the UK Office for National Statistics reported that 82% of primary school and 99% of secondary school students had SARS-CoV-2 antibody levels higher than threshold levels and only 6% of the children aged 5–11 years had received at least one dose of the COVID-19 vaccine [67]. Similarly, another survey by the UK Office for National Statistics reported 7.9 and 6.2% of children suffered from at least one symptom 4–8 weeks and 12–16 weeks post-infection, respectively [68]. Similarly, in Italy, a study consisting of 129 children < 18 years reported the prevalence of long COVID in 58.2% patients. Also, 35.7% of the patients suffered from at least one to two symptoms while 22.5% had three or more [69]. The most common symptoms reported were insomnia and respiratory symptoms such as chest pain and tightness [69]. Studies from various other countries have also reported long COVID though evidence is largely heterogenous and one of the barriers in prediction of progression to long COVID is difficult to make [58].

Mitigation techniques are not being followed or have been abandoned altogether, with poor ventilation at schools and day-care centers further contributing to the spread of infection among children [70–72].

Multisystem inflammatory syndrome in children has been the most common cause of intensive care unit admissions. A systematic review reported gastrointestinal, dermatologic and cardiovascular manifestations as well as elevated levels of CRP, IL-6 and fibrinogens in 75% of the patients [73]. Long COVID, however, remains a more prominent complication with long-term consequences and severely affecting the quality of life. In a survey in children aged 0–14 years in Denmark, the most common symptoms reported across all age groups 2 months post-infection were mood swings, rashes and troubles with

concentration and memory [74]. Symptoms observed in adults such as fatigue, post-exertional malaise, memory loss and headaches were also observed in children [74]. Liver injury has also been recorded, with two infants presenting with acute liver failure [75]. Besides this, brain hypometabolism, similar to that in adult long COVID patients [76], and long-term pulmonary dysfunction [77] have also been reported in children with long COVID.

OVERCOMING OBSTACLES: ENHANCING THE EFFECTIVENESS OF SURVEILLANCE SYSTEMS

RNA viruses possess the maximum pandemic potential [78, 79] due to their compact genome structure and high mutation rates. In order to prevent future pandemics, effective surveillance needs to be established [79, 80] for the various viruses that could pose a threat in the coming times. This would enhance controlling their spread in case zoonotic emergence is detected and aid in pandemic preparedness. Similarly, the surveillance for SARS-CoV-2 needs to be robust and consistent due to the continuous evolution of the virus, with a rate of two mutations per month being observed [81], resulting in the virus constantly improving its ability to evade immunity and transmissibility, leading to a higher risk of infections [82]. For example, the basic reproduction number (R_0) of the Delta variant has been reported to be between 3.2 and 8 [83], with Omicron being ~3.2 times higher [84]. Genomic surveillance allows researchers to track the circulating variants in a population as well as detect polymorphisms that occur frequently, allowing rapid characterization of infectivity, transmissibility and severity [69].

Dedicated data sharing has been critical to accelerating COVID-19 research, increasing the visibility of data and information and allowing researchers and clinicians to react quickly to the rapidly changing behavior of the SARS-CoV-2 virus. The Global Initiative on Sharing Avian Influenza Data (GISAID) initiative has been crucial during the peak of the pandemic, allowing researchers across the world access to high-quality, curated data [85]. As of August 2023, 15.9 million SARS-CoV-2 genome sequences have been submitted to GISAID. Similarly, platforms like EMBL's COVID-19 Data Portal [86] and NCBI SARS-CoV-2 Resources (https://www.ncbi.nlm.nih.gov/sars-cov-2/) also provided open access information to researchers, with access to various types of data, ranging from gene sequences to literature. Nextstrain [87] allowed for near real-time tracking of viral evolution through the integration of data collected from various sources, their analysis and visualization. Despite this, open-data sharing remains limited due to research organizations being skeptical of giving up control of data due to privacy concerns, publication priorities or IP ownership and exclusivity. Thus, a centralized, open-data sharing system is required with methods in place to incentivize open-data sharing and changing success metrics during a global pandemic to prompt open-data sharing.

Another shortcoming to translational research during the pandemic to quickly discover potential treatment options was the lack of resources and infrastructure, especially in LMICs and LICs. High-containment facilities and animal testing facilities in particular were lacking [88]. The establishment of these facilities would massively improve preparedness in translational research and several countries have built or are committed to building facilities in order to improve preparedness and conquer the challenges faced that caused delays in research [89].

ADVANCEMENTS IN MEDICATIONS AND THERAPEUTICS: INNOVATIONS AND IMPACT ON HEALTHCARE DRUG REPURPOSING

The most rapid response to an emerging wave of a new SARS-CoV-2 variant is repurposing existing, approved drugs. Several drugs throughout the pandemic have been repurposed for treatment using therapeutic agents such as chloroquine, hydroxychloroquine, remdesivir, ivermectin, azithromycin, dexamethasone as well as immunotherapeutic agents such as tocilizumab, casirivimab, mavrilimumab, baricitinib and others. A review, which evaluated various repurposed drugs and their effectiveness against COVID-19 in clinical trials, reported that only remdesivir, dexamethasone, tocilizumab and baricitinib displayed significant relief against COVID-19 [90]. Henceforth, a unified strategy and validation method for COVID-19 drug repurposing discovery is also required. Drug toxicity also needs to be taken into consideration since arrhythmic events have been reported in clinical trials, particularly in patients with cardiac comorbidities [91, 92], specifically in hydroxychloroquine and chloroquine [93].

Since the virus is constantly evolving, it has developed resistance to conventional antivirals [94]. New possible options are urgently needed, and several have been reported, including adapalene, levocabastine, dihydrotachysterol, bexarotene, amoxicillin, clavulanate, cysteamine and others, of which apilimod is currently being tested (NCT04446377) [95–98].

The use of bioinformatic tools and methodologies has been significant in drug repurposing as well as drug discovery with AI/ML-based methods, especially proving to be an effective method. With the large amount of data being collected and publicly available, there are sufficient data to analyze and train AI/ML models to identify both existing and new drug candidates against COVID-19. A notable example is the use of AI-assisted modeling to discover baricitinib as a therapeutic agent against COVID-19 [99], whose clinical effectiveness was later confirmed [100, 101]. Graph convolution network variations (GCN) have also been utilized for drug repurposing, with bipartite GCNs for prediction being proposed, utilizing drug, disease and protein-level information fusion as features for prediction [102]. In order to effectively predict drug response in cancer cell lines, Liu *et al.* [103] developed a deep-learning model to model drug molecules and predict drug response, combining it with genomic, transcriptomic and epigenomic networks.

REVOLUTIONIZING ANTIVIRAL TREATMENT: ADVANCES IN NOVEL ANTIVIRAL DEVELOPMENT

Effective antiviral treatment candidates against COVID-19 have been far and few. A combination therapy of baricitinib and remdesivir has been the only one to display significant pharmacological benefits [104], though uncertainty remains. The efficacy of remdesivir, for example, is reduced by the presence of an exonuclease-based proofreader, which removes the remdesivir molecules incorporated into the viral RNA during replication [105]. Despite this, the number of effective antivirals against COVID-19 remains low and the need for effective candidates is required as the virus continues to evolve. Wang *et al.* [104] discovered Hepatitis C virus inhibitors ombitasvir and pibrentasvir as potential combination therapy through both polymerase and exonuclease inhibition.

Recently, a combination therapy of nirmatrelvir and ritonavir, called Paxlovid, developed by Pfizer was approved by the United States Food and Drug Administration (US FDA) [106] and later by the UK [107] and the EU [108]. Alternatively, plant-derived secondary metabolites such as polyphenols and sesquiterpenes are considered to possess antiviral properties [109, 110]. The effect of pomegranate peel extract was investigated in disrupting the interaction between the human angiotensin-converting enzyme 2 receptor (ACE2) and the SARS-CoV-2 spike glycoprotein, as well as the activity of 3C-like protease ($3CL^{pro}$) on human cell lines, and displayed 51% binding inhibition and 3CL protease inhibition by 80% at 0.2 mg/ml [111].

Monoclonal antibody and immunomodulator development

There is also a need for novel mAbs, which have been immensely successful in treating people with severe COVID-19 complications, but due to rapidly emerging newer variants with increased fitness, partial or full resistance against mAbs is expected. The resistance of emerging Omicron variants (BA.4.6, BA.2.75.2, BJ.1 and BQ.1.1) against mAbs has been widely reported [112, 113], with BQ.1.1 being resistant against all currently approved mAbs [7]. Two novel neutralizing antibodies (nAbs), XG81 and XG83, were isolated from the plasmablast B cells of COVID-19 patients which displayed effective neutralization of the virus. When compared against nine other nAbs, XG83 demonstrated higher receptor-binding domain (RBD) affinity and possessed broad neutralization capability [114].

Effective broad-spectrum nAbs have been sporadic, with several promising nAbs currently undergoing preclinical development. Most of the discovered antibodies to date target the RBD [115]. Class 1 nAbs work by preventing binding of the S protein to the ACE2 receptor. One of the few class 1 nAbs, S2E12, has displayed broad neutralizing potential, possessing the ability to neutralize all current variants of concern (VOCs) [116, 117]. Similarly, S2K146 also demonstrated effective neutralization breadth against SARS-CoV, SARS-CoV-2 and other sarbecoviruses [118]. Several nAbs such as S309 bind to conserved regions of the virus and confer broad-spectrum activity which neutralizes Omicron subvariants BA.1, BA.1.1, BA.2 [119] and LY-CoV1404 (bebtelovimab) which neutralizes most VOCs and Omicron sublineage BA.2, and has been granted emergency use authorization by the FDA [120].

Polyclonal antibodies (pAbs) are also being currently tested against Omicron variants, with some displaying positive results. Lusvarghi *et al.*[121] prepared two pAbs, called anti-COVID-19 hyperimmune intravenous immunoglobulin (anti-COVID-19 hIVIG) and immunoglobulin G (IgG) Emergent, displaying enhanced neutralization efficacy against the D614G mutation variants but lower activity compared to authorized mAbs which have since been made redundant due to the evolution of SARS-CoV-2 virus. Different approaches to improve antibody function is to develop broad-spectrum nAbs that have the ability to simultaneously and synergistically bind to multiple epitopes as well as combining several broad-spectrum nAbs that target different domains could also be effective. Finally, to make sure that the nAbs are future-proof, targeting the conserved region of the virus would assist greatly in both broad-spectrum nAb and could aid in vaccine development.

The interest in immunomodulatory therapies and their efficacy has been intense due to the delayed onset of life-threatening symptoms, most commonly CSS. Clinicians have advised early intervention and treatment and thus, glucocorticoids have been used extensively in patients with CSS and respiratory failure [122]. However, there are still concerns about secondary infections caused by immunosuppression, a glucocorticoid side effect and COVID-19 aggravation of lung injury [123]. Therefore, other immunomodulators such as Janus kinase (JAK) inhibitors, interferons and cytokine modulators are an option (Table 1). An IL-1 receptor antagonist, Anakinra, has also been considered and a meta-analysis displayed its efficacy in COVID-19 patients, reducing the risk for mechanical ventilation and risk of death as well as the risk of adverse side effects [124]. JAK inhibitors have especially shown to be effective, with the abovementioned baricitinib being a potent JAK inhibitor and has shown extensive efficacy against COVID-19. Heparin has also been used during the pandemic as an anticoagulant to treat coagulopathy associated with severe COVID-19 [125] and has displayed evidence to inhibit SARS-CoV-2 [126].

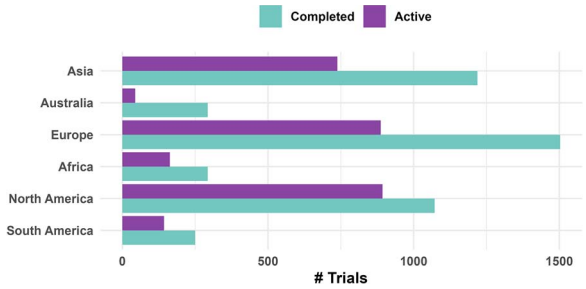


Figure 4: Number of registered clinical trials related to SARS-CoV-2 on ClinicalTrials.gov.

Alternatively, micronutrient supplementation has also been suggested since micronutrients such as vitamin C, D and zinc are known to play a role in immunomodulation. Jandaghi and colleagues evaluated 19 studies on the impact of micronutrient supplementation against COVID-19 and its effectiveness. The group concluded that high-dose supplementation of vitamin C, D and zinc may be beneficial in alleviating COVID-19 complications, such as elevated inflammatory markers, requirement of oxygen therapy, hospitalization and mortality [132]. However, these are initial results and further clinical studies are required to identify effectiveness and safe dosages.

Promising endeavors and future perspectives

Much like with other disorders and diseases, the approaches to COVID-19 etiology, prevention, diagnostics and treatment have changed. Advances in biotechnology and computational biology have enabled us to analyze large amounts of data and develop technologies based on a deeper, better understanding as well as create drugs that target specific components of the viral cell, thereby resulting in fewer adverse effects. As of now, most new therapeutic technologies are in the preclinical stages of study, with few in clinical trial stages (Figure 4). Several examples of promising technologies are described below that translate our understanding of COVID-19 into the development of therapeutics.

Omics-based studies have expedited the process of identifying several genes and proteins that played crucial roles in disease pathogenesis of COVID-19. Besides surveillance, genomics has additionally helped in determining the effects of SARS-CoV-2 infection on the immune system [81, 133] and the prognosis of COVID-19. The genetic sequences of more than 14 million B- and T-cell receptors (BCR and TCR) isolated from COVID-19 patients were investigated, and discovered that patients affected by serious

Table 1. List of promising immunomodulatory therapies currently under preclinical development

Name	Description	Reference
Niclosamide	Causes inhibition of inflammasomes and SARS-CoV-2 through autophagy induction	[127]
Anakinra	IL-1 antagonist, particularly effective in hospitalized patients suffering from acute-respiratory distress syndrome (ARDS)	[124]
Thymosin-α1	Inhibits inflammatory activation of monocytes and myeloid dendritic cells (mDc) through inactivation of mediators TNF-α, IL-6 and IL-8	[128]
Interferon-α2b	Effective immune neutralization in hospitalized patients, decreasing risk of pneumonia and lung injury, while increasing SpO_2 levels. Further investigation is needed	[129, 130]
Tofacitinib	Limits JAK1 and JAK3 enzymes, thus inhibiting the JAK–STAT pathway. Led to decreased mortality in hospitalized patients in a 28-day randomized double-blind, randomized clinical trial	[131]

complications requiring oxygen therapy had a higher number of somatic mutations in BCRs [134]. Similarly, proteomic studies allowed the integration and analysis of interacting proteins and thus revealed the underlying pathogenesis of the disease. Proteomic analysis of seven organs from 144 autopsies ascertained 5336 altered proteins when compared to the control. Dysregulation of key factors involved in major processes such as hypoxia, blood coagulation, fibrosis and angiogenesis were observed in multiple organs [135].

Comparative transcriptomics revealed robust SARS-CoV-2 infection in HEK293T cells without triggering an immune response, instead causing activation of pathways related to endoplasmic reticulum stress and unfolded protein response, which may be the cause of major SARS-CoV-2 symptoms such as metabolic disruption and inflammation [136]. In addition, the expression of hACE2 had direct correlation to viral load but does not scale to immune response and only cells with high expression of ACE2 mounted an immune response [136].

Demichev and colleagues analyzed the plasma proteomes of 139 COVID-19 patients through flow chromatography, tandem mass spectrometry, sequential window acquisition of all theoretical fragment ion spectra mass spectrometry and deep-neural network. Eleven proteins and nine clinical parameters were included in the prediction model of disease progression to identify early infected individuals and classify them accordingly based on risk [137], but translation to clinical settings requires additional validation and testing before progression to clinical testing. Typically, lengthy processes such as studying disease pathogenesis, identification of small molecules and antibody design have been shortened through omics-based technologies. Clustered Regulatory Interspersed Short Palindromic Repeats (CRISPR)-Cas-based diagnostics are currently available. They are highly sensitive, quick and accurate in SARS-CoV-2 detection. These assays are based on various CRISPR-Cas enzymes such as cas13 (SHERLOCK and CREST), cas12a (AIOD-CRISPR, DETECTR, VaNGuard), cas9 (FELUDA) and cas3 (CONAN) [138–144]. Besides diagnostics, CRISPR-Cas has also been suggested as a potential therapeutic protocol. The Prophylactic Antiviral CRISPR in Human Cells system as well as 40 CRISPR RNAs (crRNAs) target conserved regions in SARS-CoV-2 and cause degradation viral RNA, effectively inhibiting viral replication. The crRNAs reported repression of signal reporters fused to RdRP and N genes by 86 and 71%, respectively [145]. Drug delivery for CRISPR-based therapeutic technologies remains a challenge although there are a variety of options that should be tested [146].

Due to advancements made in molecular biology, the number of agents undergoing preclinical testing has increased dramatically from a wide range of technologies. We could not cover all of them, though we have mentioned a few important ones that showed potential to become a viable treatment option in the future (Table 2). Nanotechnology has made a lot of progress in this regard, with mRNA-liquid nanoparticle-based vaccines currently being explored [147, 148], and one approved in Moderna's vaccine. Antiviral nanomaterials possessing virucidal properties such as polymer surfactants are also currently being explored. NanoViricides developed a topical nanoviricide called NV-CoV-2 that binds to the viral particles, ultimately encapsulating the virus and dismantling it without any involvement of the immune system [149]. Similarly, other technologies such as nanodecoys and the incorporation of nanotechnological methods with traditional treatment methods are being explored to improve upon them [150], and there have been some successes, especially in terms of rapid diagnosis and treatment. Recently, a novel viral RNA extraction method was developed using poly with carboxyl-group-coated magnetic nanoparticles, allowing for rapid and sensitive extraction of SARS-CoV-2 in less than 9 min [151]. Another study developed a lateral flow immunoassay kit by modifying the SARS-CoV-2 nucleoproteins with selenium nanoparticles (NPs), allowing swift identification of anti-SARS-CoV-2 antibodies IgG and IgM, in the human blood in under 10 min [152]. Various NPs, especially silver (Au) and gold (Ag), are being investigated as potential antiviral agent. A study observed that AuNPs of 10 nm in diameter with concentrations of 1–10 ppm were effective in inhibiting extracellular SARS-CoV-2 [153]. Similarly, zinc-oxide NPs displayed inactivation of both the Delta and Omicron variants at 20 mg/ml [154].

DISCUSSION AND CONCLUSION

In this review, we discussed various factors currently preventing the successful alleviation of SARS-CoV-2 infections in the face of the constant evolution of the virus as well as methods of treatments currently being pursued. Access to vaccines and, more importantly, updated boosters across the world and mitigation techniques against new variants should be the primary goal of countries to assist in managing the virus, slowing down its evolution, and reduce death and disability in the population [169]through mask mandates and limiting mass gathering events at local levels during seasonal outbreaks. Drug repurposing remains the fastest method to introduce new treatment options,

Table 2. A brief summative list of promising therapeutic agents and vaccines currently undergoing clinical trials

Drug name	Phase of study	Description	Country
Antivirals			
Proxatulamide [155]	Phase III	Supportive treatment for COVID-19 patients to prevent complications	Brazil
Interferon β-1b + lopinavir-ritonavir + ribavirin [156]	Phase II	Early therapy to alleviate COVID-19 symptoms and reduce hospitalization duration	Hong Kong
Aprotinin [157]	Phase III	Protease inhibitor with anti-inflammatory properties, beneficial in reducing hospital stay and use of oxygen therapy	Spain
Sofosbuvir + daclatasvir [158]	Phase III	Decreased duration of hospitalization with higher cumulative rate of hospital discharge compared to control	Iran
Ruxolitinib [159]	Phase III	Treatment for acute-respiratory distress syndrome (ARDS) and cytokine storm syndrome (CSS)	Russia, United States, Brazil, Spain, Argentina, Peru, Turkey, Mexico, UK, Colombia, France and Germany
Monoclonal antibodies (mAbs)			
Infliximab [160]	Phase II	Prevention of severe COVID-19 complications through the use of TNF-α inhibition	United Kingdom
Cilgavimab + tixagevimab [161]	Phase III	Combination therapy of COVID-19, reporting 77% reduction of disease symptoms. Approved for use in the EU	United States, Latin America, Europe and Japan
Bamlanivimab [162]	Phase II	Neutralizing antibodies (nAbs) for patients with mild-to-moderate symptoms, decrease in viral load observed	United States
Tocilizumab [163]	Phase III	Reduction of multisystem organ failure and complications in patients requiring supplemental oxygen. Granted EUA in the USA	Greece
Vaccines			
Coronavirus-like particles (CoVLP) adjuvanted vaccine [164]	Phase III	Plant-based recombinant vaccine containing coronavirus-like particles (CoVLP) combined with an adjuvant	Argentina, Brazil, Canada, Mexico, United Kingdom and United States
SOBERANA 02 [165]	Phase IIb	Recombinant protein vaccine conjugated with a tetanus toxoid	Cuba
Nanocovax [166]	Phase II	Recombinant protein vaccine consisting of spike protein from CHO cells using recombinant DNA technology	Vietnam
iNCOVACC [167]	Phase III	ChAd36-SARS-CoV-2 spike recombinant intranasal vaccine	India
ARCT-154 [168]	Phase II/III	Self-amplifying RNA (saRNA) vaccine delivered in a lipid nanoparticle (LNP) encapsulation	United Kingdom

helping clinicians minimize complications and mortality rates due to the ever-changing nature of the virus. Meanwhile, it provides time for researchers to develop novel antivirals and other therapeutics that can be tested thoroughly before approval for general use to avoid unexpected side effects and minimize toxicity. Novel antivirals and mAbs remain the best solution for tackling serious SARS-CoV-2 complications in populations at risk. While significant progress is being made to understand the etiology of long COVID and develop a standardized protocol toward its prognosis, diagnosis and, ultimately, developing treatment protocols.

Since 2020, the COVID-19 pandemic has perhaps exposed our shortcomings in terms of preparedness against a potential pandemic. It has repeatedly challenged policymakers and public health experts alike and continues to do so. Enhanced surveillance has ever been so important in containing an outbreak especially with new variants emerging since it allows better response time to mobilize mitigation efforts and resources. Furthermore, countries need to have a robust surveillance system since RNA respiratory viruses carry the most pandemic potential. The rapid response from scientists and clinicians allowed for some breakthroughs, especially with the fastest vaccine development and approval in history. An interdisciplinary framework is required, in order to allow tools in virology, translational medicine, drug discovery and -omics to flourish and allow for the rapid development of novel and existing interventions in response, with constant re-evaluation in the face of a rapidly evolving virus and changing epidemiological factors. Ultimately, effective vaccines will determine the fate of a pandemic, so vaccine equity is a critical goal that the world must achieve. Regardless, pharmacological therapies will always play an important role in lowering mortality rates and illness consequences.

Key Points

- Emergence of SARS-CoV-2 variants displaying increased fitness and transmissibility challenges the efforts of translational research in the mitigation of COVID-19.
- Long-term health complications associated with COVID-19 such as long COVID and MIS-C additionally qualify for intense research interventions.
- Progress in translational research is currently impacted due to a lack of resource generation, with worldwide scaling back on genome surveillance programs, and vaccine and drug development.
- The availability of effective treatments options and newer vaccines is being compromised, exposing the population to the currently circulating variants and increasing the risk of death and disability.
- We outline the advancements in medicine and therapeutic interventions brought about by translational research in COVID-19 along with new promising approaches currently under investigation as future perspectives of translational research in the fight against SARS-CoV-2.

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DATA AVAILABILITY

Data and scripts used for creating all the figures is publicly available at https://github.com/nityendra21/COV19_review_supp.

AUTHOR CONTRIBUTIONS

Conceptualization: J.N., R.P. Writing—original draft preparation: N.S., U.S. Writing—editing and review: R.P., J.N., U.S., N.S., P.A. Visualizations: N.S., U.S., P.A. Supervision: R.P., J.N. All authors have read and agreed to the published version of the manuscript.

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