Therapeutic Strategies in the Development of Anti-viral Drugs and Vaccines Against SARS-CoV-2 Infection

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Abstract
The whole world is currently facing a pandemic of an infectious disease known as novel coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This outbreak emerged unexpectedly and imposed a potential threat to humans, associated with the social and economic burden on the individual and federal governments. COVID-19, which initially started in Wuhan City of China and then spread to the whole world, has been declared a Public Health Emergency of International Concern. The continuous increase in the number of confirmed cases leads to high mortality across the world. Growing evidence indicates that the mortality rate is very predominant in elderly people and those with preexisting health conditions. However, the potential pathogenesis of SARS-CoV-2 infection in humans is still unknown. The dysregulated/exuberant immune response may have substantially contributed to the SARS-CoV-2-mediated pathology. Nevertheless, there is no clinically approved drug/vaccine currently available that can restrict its pathogenesis. However, several drugs are currently shown to provide some therapeutic benefits for COVID-19 patients, including antiviral drugs that might have a significant role in restricting the current pandemic of COVID-19. In this article, we highlighted the pharmacological treatment strategies for COVID-19 and purposed the therapeutic targets for the development of vaccines or anti-viral drug molecules against SARS-CoV-2 infection in humans.

Keywords
Novel coronavirus disease · COVID-19 · SARS-CoV-2 · Anti-viral drugs · Vaccine · Clinical trials

Introduction
In the past 2 decades, three coronavirus (CoV) outbreaks occurred in the world [1]: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 [2, 3], Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [4], and SARS CoV-2 in 2019 [5]. The SARS-CoV epidemic emerged from an animal market in the Guangdong province of China.
and spread to 32 countries through air travel routes, infecting 8422 individuals and 916 (10.87%) casualties from November 2002 to August 2003 [6, 7]. MERS-CoV was first reported to cause human infection in Saudi Arabia in 2012, where it remains a major public health concern, and spread over 27 countries, infecting a total of 2,494 individuals and claiming 868 (34.77%) fatalities during the period April 2012 to December 2019 [4, 7, 8].

The recent outbreak of coronavirus disease 2019 (COVID-19) started in December 2019 in Wuhan City of China and spread through human-to-human transmission across the world [9–11]. It continues to cause severe infections in humans, posing significant threats to global public health. China initially reported to the World Health Organization (WHO) on December 31, 2019. Further, on March 11, 2020, the WHO declared COVID-19 a pandemic and imposed Public Health Emergency of International Concern [12]. The fatality rate of coronavirus MERS-CoV was (34.77%) higher than that of SARS-CoV (10.87%); however, SARS-CoV-2 transmitted rapidly in comparison to SARS-CoV and MERS-CoV [13] and accounts for 3.4% deaths all over the world [14]. The mortality rate of COVID-19 varies from one country to another. However, these fatality rates also vary with the age range of the infected persons. COVID-19 primarily spread through respiratory droplets. The manifestation of SARS-CoV-2 infections ranges from fever, cough, shortness of breath, fatigue, and, in a small population of patients, gastrointestinal infection symptoms to acute respiratory distress and pneumonia [15–17]. The loss of taste (ageusia) and loss of smell (anosmia) as one of the major symptoms of COVID-19 was initially ignored. However, further studies demonstrated a significant presence of ageusia and anosmia in the patients with COVID-19 infection [18–20]. The reproductive number of SARS-CoV-2 infection is estimated to be 2–3 [11], and the elderly people with underlying complications such as diabetes, heart disease, lung disease, cancer, etc. are more susceptible to severe infection and fatality [21–24]. Currently, there is no clinically approved drug/vaccine for the treatment of this disease. All the health organizations across the globe are on high alert and treating COVID-19 patients with the available drugs used in other respiratory infections. However, several potent candidates of antivirals and repurposed drugs are under urgent investigation [9]. This article highlighted the recent updates on the epidemiology, antiviral drugs used, and possible therapeutic strategies for the development of a vaccine against SARS-CoV-2 pathology.

Epidemics of COVID-19

According to recent WHO updates, globally, there are about 18 million confirmed cases and rising in American, European, and Southeast Asian countries [14]. To date, 216 countries and territories have been affected by the COVID-19 pandemic with a 5.9% mortality rate estimated by the WHO. Although the disease is now better contained in the suspected origin, the USA has witnessed the biggest surge in coronavirus cases over the past few months which accounts for around one quarter of the total number of infections worldwide. The USA, Brazil, and India are the most affected countries, contributing about half of the COVID-19-infected people across the world [14]. European countries witnessed the maximum number of coronavirus-related deaths than any part of the world followed by the USA. However, the actual total death toll may be higher than the number of confirmed deaths, due to limited testing and problems in the attribution of the cause of death and the difference between reported confirmed deaths and total deaths that varies by country to country. Surprisingly, men are at a significantly higher risk of having severe symptoms and fatalities, compared to women [14]. A maximum number of infected individuals are in the age group of 21–45 years; however, the fatalities are more in elderly patients, i.e., above 60 years. If the current situation prevails for a longer duration and no therapeutic drug/vaccine is available, it is expected that almost one third of the world population may get infected and millions of deaths occur, worldwide.

Etiology of COVID-19

The coronaviruses belong to a large subfamily, Orthocoronavirinae, of the Coronaviridae family within the Nidovirales order and are classified into 4 genera: Alpha (α), Beta (β), Gamma (γ), and Delta (δ) coronavirus. They are single-stranded RNA viruses (+ssRNA) genomes with the size ranging from 26 to 32 kilobases, with a crown-like appearance due to the presence of spike glycoproteins on the envelope. They are known to infect both humans and animals. SARS-CoVs, MERS-CoVs, and SARS-CoV-2 are classified as β-coronavirus family members [25]. There are structural similarities between the MERS-CoV and SARS-CoV; however, they target the host cells through different receptors, dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) respectively [26, 27]. The coronavirus particle, virion, consists of a nucleocapsid, containing single-stranded genomic RNA and phosphorylated nucleocapsid (N) protein, which is covered inside the phospholipid bilayers having two different types of spike proteins (Fig. 1), the spike glycoprotein trimmer (S) that is present in almost all the CoVs and the hemagglutinin-esterase (HE) that is found in few CoVs. The membrane (M) and envelope (E) proteins are located among the S proteins in the virus envelope [28]. SARS-CoV-2 is a positive-sense, single-stranded RNA virus containing 29,891 nucleotides, encoding for 9860 amino acids [29]. Although its origin is not entirely understood, the genomic
analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats [30].

Recently, bioinformatic analysis of a virus genome from a patient with COVID-19 shows that the genome of SARS-CoV-2 shows 89% nucleotide identity with batSARS-like-CoVZXC21 and 82% with that of human SARS-CoV [29]. The phylogenetic trees of their orf1a/b, spike, envelope, membrane, and nucleoprotein also clustered closely with those of the bat, civet, and human SARS coronaviruses. Further, additional genomic studies suggest that SARS-CoV-2 shared 79% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV [31, 32]. Figure 2 shows the comparative analysis of the genomic organization of various coronaviruses in different species. All these studies indicated a high genetic homology among SARS-CoV-2, MERS-CoV, and SARS-CoV. SARS-CoV-2 uses the same receptor, angiotensin-converting enzyme 2 (ACE2), as that for SARS-CoV to enter the target cell, and mainly spreads through the respiratory tract. ACE2 enzyme is involved in the regulation of blood pressure and is expressed by cells of the heart, lungs, kidneys, and intestines. SARS-CoV-2 binds to ACE2 through spike proteins. However, the external subdomain of the spike’s receptor-binding domain of SARS-CoV-2 shares only 40% amino acid identity with other SARS-related coronaviruses [29]. So, the drugs targeting SARS-CoV and MERS-CoV might not be fit for the prevention of COVID-19.

Current Scenario of Possible Therapeutic Drugs Against SARS-CoV-2 Infection

To date, we do not have any clinically approved antiviral drug or vaccine that can cure this disease. However, the battle to find a specific therapy for the recent pandemic of COVID-19 is still going on. Currently, various preventive measures including social distancing, hand sanitization, avoiding non-essential international/national travels, use of facial masks, etc. are used to restrict the further transmission of SARS-CoV-2 infection across the world. Several pharmacological treatment possibilities are being explored to treat this infection. In the current situation of COVID-19 pandemic, possible repositioning of various antiviral and antiparasitic drugs including hydroxychloroquine and chloroquine, remdesivir, protease inhibitors—lopinavir and ritonavir, etc. previously used for SARS and MERS or other viral infections is now being followed to treat SARS-CoV-2 infection and might have gained significant improvement in pneumonia-associated symptoms of some of the COVID-19 patients [9, 33–38].

Table 1 shows the clinical trials of repurposing various drugs as a possible therapeutic strategy against SARS-CoV-2 infection. Remdesivir, a nucleotide analog, is a broad-spectrum antiviral drug that inhibits RNA replication [30] and may be a promising anti-viral drug therapy for COVID-19. Several studies demonstrated the effectiveness of
remdesivir in animal models of SARS-CoV-2-related coronaviruses [30, 39–41]. However, it was less effective against ebolavirus infections in humans [42]. Recently, clinical trials of remdesivir against COVID-19 are ongoing primarily in the USA and China [43].

Hydroxychloroquine is FDA-approved to prevent and treat malaria, as well as to treat the autoimmune diseases rheumatoid arthritis and lupus [44–48]. Some preliminary reports have suggested that hydroxychloroquine, alone or in combination with the FDA-approved antibiotic azithromycin, may benefit people with COVID-19. Numerous clinical trials are planned or underway, including a recently launched study supported by NIH’s National Heart, Lung and Blood Institute, evaluating the safety and effectiveness of hydroxychloroquine for treatment of adults hospitalized with COVID-19.

The preliminary studies indicate that chloroquine and hydroxychloroquine have the potential to improve disease outcomes and possibly slow COVID-19’s progression [49]. Other in vitro and clinical studies demonstrated that the antiviral action of hydroxychloroquine might be effective in limiting SARS-CoV-2 infection [49, 50]. Further, a combination of hydroxychloroquine and azithromycin has also been used against the pathophysiology of COVID-19 [51] and is under clinical trial against SARS-CoV-2.

The chloroquine drug appears to interfere with terminal glycosylation of ACE2 and exerts direct antiviral effects by inhibiting pH-dependent steps of the replication in several viruses including coronaviruses showing a strong impact on SARS-CoV infection [52–55]. Moreover, chloroquine and hydroxychloroquine are known to modulate the immune response in some infectious diseases via inhibition of autophagy, controlling Toll-like receptor (TLR) signaling, and diminishing the cytokine storm by suppressing the production of TNF-α and IL-6 [52, 56] and worked at both entry and post-entry stages of the COVID-19 infection [35]. Currently, we are looking for therapeutic strategies to counter the severe effects of the SARS-CoV-2 infection. A preliminary clinical trial of chloroquine repurposing against SARS-CoV-2 infection has shown some positive results, which led to the start of several clinical trial studies across the world [35, 37]. Recently, the National Institutes of Health (NIH), USA, stopped the clinical trial of hydroxychloroquine as a potential therapy for COVID-19 because some studies show controversial results of this drug against SARS-CoV-2 [57]. Through the fog of alleged misconduct, hope, hype, and politicization that surrounds hydroxychloroquine, the malaria drug touted as a COVID-19 treatment, a scientific picture is now emerging. Recent systematic studies demonstrated no significant benefit of hydroxychloroquine drug in COVID-19 treatment [57, 58].

Besides, the clinical trials of a combination of two anti-HIV drugs—lopinavir and ritonavir—have also been started for these drugs against the SARS-CoV-2 pathology [59]. These drugs are used in a fixed-dose combination for the treatment and prevention of HIV/AIDS [60]. A recent study reported that the β-coronavirus viral loads of a COVID-19 patient in Korea were significantly reduced after lopinavir/ritonavir treatment [61]. In contrast, another clinical trial on hospitalized adult patients with severe COVID-19 shows no benefit with the lopinavir-ritonavir treatment [62].

In the past, vaccines were developed against SARS-CoV and MERS-CoV, but none of them has been clinically approved for use in humans [63]. Currently, several vaccination strategies have been undergoing against SARS-CoV using vaccine candidates including inactivated virus, a live-attenuated virus, viral vectors, subunit vaccines, recombinant proteins, DNA vaccines, etc. across the world. Additionally, many other options are being explored for the treatment of
| No. | Title                                                                 | Status             | Conditions                                                                 | Interventions                                                                                                                                                                                                 | Locations                                                                                      |
|-----|----------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 1   | Maternal-Foetal Transmission of SARS-CoV-2                          | Recruiting         | Maternal fetal infection transmission SARS-CoV 2                           | Diagnostic test: diagnosis of SARS-CoV2 by RT-PCR and IgG, IgM serologies in the amniotic fluid, the blood cord, and the placenta                                                                 | • CHR Orléans, Orléans, France                                                               |
| 2   | COVID-19 Breastfeeding Guideline for African-Americans              | Not yet recruiting | COVID-19 Exclusive breastfeeding                                           | Behavioral: COVID-19 breastfeeding support                                                                                                                                                                | • Meharry Medical College, Nashville, TN, USA                                                  |
| 3   | Comparison of the Efficacy of Rapid Tests to Identify COVID-19 Infection (CATCH COVID-19) | Not yet recruiting | COVID-19                                                                     | Diagnostic test: diagnostic tests for COVID-19 infection                                                                                                                                                  |                                                                                               |
| 4   | The Role of a Private Hospital in Hong Kong Amid COVID-19 Pandemic   | Active, not recruiting | COVID                                                                      | Diagnostic test: COVID 19 diagnostic test                                                                                                                                                                 | • Hong Kong Sanatorium & Hospital, Hong Kong, Hong Kong                                      |
| 5   | Lung CT Scan Analysis of SARS-CoV2 Induced Lung Injury              | Recruiting         | COVID-19                                                                    | Other: lung CT scan analysis in COVID-19 patients                                                                                                                                                           | • Ospedale Papa Giovanni XXIII, Bergamo, Italy                                                |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • Policlinico San Marco-San Donato group, Bergamo, Italy                                      |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy                                |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • ASST di Lecco Ospedale Alessandro Manzoni, Lecco, Italy                                     |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • ASST Melegnano-Martesana, Ospedale Santa Maria delle Stelle, Melzo, Italy                   |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • ASST Monza, Monza, Italy                                                                    |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • AUSL Romagna-Ospedale Infermi di Rimini, Rimini, Italy                                     |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • Istituto per la Sicurezza Sociale-Ospedale della Repubblica di San Marino, San Marino, San Marino                                     |
|     |                                                                     |                    |                                                                             |                                                                                                                                                                                                            | • Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates                                |
| 6   | Study Evaluating the Safety and Efficacy of Autologous Non-hematopoietic Peripheral Blood Stem Cells in Covid-19 | Completed          | Coronavirus disease 2019 (COVID-19)                                      | Biological: autologous non-hematopoietic peripheral blood stem cells (NHPBSC) Drug: COVID-19 standard care Device: performance evaluation study of RealDetect™ COVID-19 RT-PCR Kit for COVID-19 detection | • Institute of Epidemiology, Disease Control and Research (IEDCR), Mohakhali, Dhaka (for sample collection and sample storage), Institute for Developing Science & Health Initiatives (ideSHI); Mohakhali, Dhaka (for sample analysis, data collection, data analysis), Dhaka, Bangladesh |
| 7   | Performance Evaluation of RealDetect™ COVID-19 RT-PCR Kit for the Detection of SARS-CoV-2 Virus | Recruiting         | High sensitivity and specificity (with 95% confidence interval) of RealDetect™ COVID-19 RT-PCR Kit |                                                                                                                                                                                                            | • UHmontpellier, Montpellier, France                                                           |
| 8   | Diagnostic Value of Patient-Reported and Clinically Verified Olfactory Disorders (COVID-19) | Completed          | COVID-19                                                                   | Biological: reporting of anosmia, ageusia, and other clinical symptoms                                                                                                                                       | • ASST Monza-Ospedale San Gerardo, Monza, Italy                                               |
| 9   | Smell and Taste Disorders in COVID-19 Patients                      | Recruiting         | COVID-19                                                                   | Other: investigation of smell and taste disorders                                                                                                                                                         | • Imperial College, London, UK                                                                |
| 10  | Neonatal Complications of Coronavirus Disease (COVID-19)            | Recruiting         | Neonatal COVID-19 disease                                                  | Other: no intervention—exposure is to COVID-19                                                                                                                                                            | • CHU Amiens, Amiens, France                                                                 |
| 11  |                                                                     | Recruiting         |                                                                            |                                                                                                                                                                                                            |                                                                                               |
| No. | Title                                                                                     | Status                     | Conditions                                      | Interventions                                         | Locations                                                                 |
|-----|-------------------------------------------------------------------------------------------|----------------------------|--------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------|
| 12  | COVID-19 Prevalence and Cognitive Deficits in Neurological Patients                       | Not yet recruiting         | Neurological diseases or conditions Stroke, acute Seizure disorder | Diagnostic test: COVID-19 swap test PCR                 | • Aalborg University Hospital, Aalborg, DK, Denmark                      |
|     |                                                                                           |                            |                                                  |                                                       | • Aarhus University Hospital, Aarhus, DK, Denmark           |
|     |                                                                                           |                            |                                                  |                                                       | • Regional Hospital West Jutland, Høstebro, Holstebro, DK, Denmark |
|     |                                                                                           |                            |                                                  |                                                       | • Regional Hospital Central Jutland, Viborg, Viborg, DK, Denmark |
| 13  | Frailty in Elderly Patients with COVID-19                                                  | Recruiting                 | COVID-19                                        | Other: relation between frailty and clinical outcomes in elderly patients with COVID-19 | • ASST Monza-Ospedale San Gerardo, Monza, Italy                   |
| 14  | COVID-19 Convalescent Plasma (CCP) Transfusion                                             | Recruiting                 | COVID-19                                        | Biological: COVID convalescent plasma                  | • University of Mississippi Medical Center, Jackson, MS, USA        |
| 15  | COVID-19 in the Swedish ICU-Cohort: Risk Factors of Critical Care Admission and Intensive Care Mortality | Not yet recruiting         | COVID-19 Critical illness                       | Other: COVID-19 and intensive care                     |                                                                          |
| 16  | MURDOCK Cabarrus County COVID-19 Prevalence and Immunity (C3PI) Study                    | Enrolling by invitation    | COVID-19                                        | Other: COVID-19 PCR and serology testing               | • Duke CTSI Translational Population Health Office, Kannapolis, NC, USA |
| 17  | Rapid Diagnostic Test for COVID-19 Based on Antibody Detection (YCOVID)                    | Active, not recruiting     | COVID-19                                        | Diagnostic test: ELISA and Rapid test to detect antibodies against COVID-19 | • Parc Tauli University Hospital, Sabadell, Barcelona, Spain       |
| 18  | The Assessment of the Prevalence, Clinical Course and Treatment of COVID-19 Complications | Enrolling by invitation    | Coronavirus infection SARS-CoV-2 Complications  | Other: complex diagnostic panel                        | • Silesian Centre for Heart Disease, Zabrze, Silesia, Poland       |
| 19  | COVID-19-Convalescent Plasma for Treating Patients with Active Symptomatic COVID 19 Infection (FALP-COVID) | Recruiting                 | COVID-19 infection Cancer patients General population | Biological: convalescent plasma from COVID-19 donors | • Fundacion Arturo Lopez Perez, Providencia, Santiago, Chile         |
| 20  | COVID-19 Endoscopy Survey                                                                  | Completed                  | COVID-19                                        | Other: practice details                                | • Kings County Hospital Center, Brooklyn, NY, USA; Albertson, NY, USA |
|     |                                                                                           |                            |                                                  |                                                       | • Faculty of Medicine, Zagazig University, Zagazig, Sharkia, Egypt |
|     |                                                                                           |                            |                                                  |                                                       | • Al-Azhar University, Cairo, Egypt                              |
|     |                                                                                           |                            |                                                  |                                                       | • Ahvaz Imam hospital, Ahvaz, Iran, Islamic Republic of        |
|     |                                                                                           |                            |                                                  |                                                       | • Cliniques Universitaires Saint Luc, Brussels, Belgium         |
| 21  | Survey; COVID-19 Patients Managed in the Operating Theatre of Belgian Hospitals            | Recruiting                 | COVID-19                                        | Diagnostic test: COVID-19 test, polymerase chain reaction for SARS-CoV-2 | • Rigshospitalet University Hospital of Copenhagen, Copenhagen, Denmark |
| 22  | COVID-19 Surveillance of Patients and Healthcare Workers in a Hospital Department          | Enrolling by invitation    | COVID-19                                        |                                                       |                                                                          |
| 23  | Viral Infection and Respiratory Illness Universal Study [VIRUS]: COVID-19 Registry        | Recruiting                 | Coronavirus                                      | Other: observational                                    | • Mayo Clinic in Arizona, Scottsdale, AZ, USA                     |
|     |                                                                                           |                            |                                                  |                                                       | • Mayo Clinic in Florida, Jacksonville, FL, USA                |
| No. | Title | Status/Recruiting | Conditions | Interventions | Locations |
|-----|-------|-------------------|------------|---------------|-----------|
| 24  | Predictive Factors COVID-19 Patients | Recruiting | COVID-19 | Other: predictive factors for clinical response in patients with COVID-19 | Society of Critical Care Medicine (150+ sites), Chicago, IL, USA; Rahul Kashyap, Rochester, MN, USA |
| 25  | Characteristics and Outcome of Coronavirus Disease 2019 (COVID-19) in Egypt | Not yet recruiting | Characteristic diseases Outcome, fatal | Other: follow-up | Humanitas Rozzano/San Pio X, Rozzano, Lombardia, Italy |
| 26  | Detection of Anti-COVID-19 Antibody Levels in an Hospital Population | Recruiting | COVID-19 | Diagnostic test: detection of anti-COVID-19 antibody level | Monza-Ospedale San Gerardo, Monza, Italy |
| 27  | Isotretinoin in Treatment of COVID-19 | Not yet recruiting | COVID-19 | Drug: isotretinoin only product in oral dose form | Universidade del Rosario, Bogota, Cundinamarca, Colombia |
| 28  | Convalescent Plasma for Patients with COVID-19: a Pilot Study | Not yet recruiting | Coronavirus Coronavirus infection | Drug: plasma | University of Ljubljana, Ljubljana, Slovenia |
| 29  | Slovenian National COVID-19 Prevalence Study | Recruiting | COVID-19: SARS-CoV-2 | Diagnostic test: no intervention planned due to the observational study design—only a diagnostic testing | North Shore University Hospital, Manhasset, NY, USA; Long Island Jewish Medical Center, New Hyde Park, NY, USA |
| 30  | Incidence of COVID-19 Test Conversion in Post-surgical Patients | Recruiting | SARS-CoV-2 | Diagnostic test: COVID-19 PCR and serology | Assiut University Hospitals, Assiut, Egypt |
| 31  | Novel COVID-19, a National Analysis | Recruiting | COVID-19 | Other: prevalence of COVID-19 | Clinical Research Institute Methodist Health System, Dallas, TX, USA |
| 32  | Convalescent Plasma for Patients with COVID-19: a Randomized, Open Label, Parallel, Controlled Clinical Study | Not yet recruiting | Coronavirus Coronavirus infection | Drug: plasma; Drug: hydroxychloroquine | Universidad del Rosario, Bogota, Cundinamarca, Colombia |
| 33  | Methodist Health System COVID-19 Patient Registry | Not yet recruiting | COVID-19 | Other: treatment for COVID-19 | University at Buffalo, Buffalo, NY, USA |
| 34  | Safety and Efficacy of Melatonin in Outpatients Infected with COVID-19 | Not yet recruiting | COVID-19 | Drug: melatonin; Other: placebo (methylcellulose) capsule | Medicine Invention Design Incorporation (MIDI) - IORG0007849, North Bethesda, MD, USA |
| 35  | Discovery Stage (Proof-of-Concept) COVID-19 Antigen Presentation Therapeutic Vaccine | Active, not recruiting | COVID-19 | Biological: COVID-19 therapeutic vaccine - Nucleocapsid-GM-CSF protein lactated Ringer’s injection | Beaumont Health System, Royal Oak, MI, USA; Beaumont Health, Royal Oak, MI, USA |
| 36  | Dynamic Evaluation of COVID-19 Diagnostic Tests | Not yet recruiting | COVID-19 | Diagnostic test: COVID-19 diagnostic test | Beaumont Health System, Royal Oak, MI, USA; Beaumont Health, Royal Oak, MI, USA |
| 37  | NGS Diagnostic in COVID-19 Hosts - Genetic Cause Relating to the Course of Disease Progression | Not yet recruiting | COVID-19 | Genetic: whole genome analysis; Genetic: T cell receptor (TCR) repertoire; Genetic: SARS-CoV-2 viral composition | University Hospital of Toulouse, Toulouse, France |
| No. | Title                                                                 | Status                  | Conditions                                      | Interventions                                                                 | Locations                                                                 |
|-----|-----------------------------------------------------------------------|-------------------------|-------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 40  | Minimal Invasive Autopsies to Investigate Changes in Deceased COVID-19 Patients | Recruiting              | COVID-19                                        | Procedure: CT-scan with minimal invasive autopsy                               | • Jessa Hospital, Hasselt, Belgium                                         |
| 41  | Exchange Transfusion Versus Plasma from Convalescent Patients with Methylene Blue in Patients with COVID-19 | Recruiting              | COVID-19                                        | Biological: exchange blood transfusion from normal donor                       | • Ain Shams University, Cairo, Egypt                                         |
| 42  | Clinical Characteristics and Outcomes of Pediatric COVID-19           | Recruiting              | SARS-CoV-2 infection Pediatric ALL Pneumonia, viral Pandemic response | Other: exposure (not intervention)—SARS-CoV-2 infection                       | • University of Calgary/Alberta Children’s Hospital, Calgary, Alberta, Canada |
| 43  | Relation Between Lab Finding and COVID-19 Severity                   | Not yet recruiting      | COVID-19                                        | Diagnostic test: D-dimer, CBC, ESR, CRP                                       |                                                                           |
| 44  | Setting Up a COVID-19 Care Facility at a Prison in Pakistan          | Completed               | COVID-19                                        | Other: COVID-19 facility                                                      | • Camp Jail/COVID-19 care facility/SIMS, Lahore, Pakistan                 |
| 45  | Impact of COVID-19 on Marshallese Communities in the U.S.            | Not yet recruiting      | COVID-19                                        | Other: assessing impact of COVID-19                                           |                                                                           |
| 46  | Thorax Computed Tomography Severity Score and Outcome in COVID-19 Patients | Recruiting              | COVID-19                                        | Diagnostic test: CT scan                                                      | • Tepecik Training and Research Hospital, Izmir, Izmir, Konak, Turkey      |
| 47  | Antibody Based Tests for SARS-CoV-2 COVID-19-Evaluation of Patients and Healthcare Providers in the Confinies of Healthcare Settings | Recruiting              | COVID-19                                        | Diagnostic test: CoronaCideTM COVID-19 IgM/IgG Rapid Test and Premier Biotech COVID-19 IgM/IgG Rapid Test | • St. David’s Medical Center, Austin, TX, USA                               |
| 48  | Spartan COVID-19 System: Evaluation of Clinical Sample Collection    | Recruiting              | COVID-19                                        | Device: Spartan COVID-19 System                                                | • Humber River Hospital, North York, Ontario, Canada                       |
| 49  | Classification of COVID-19 Infection in Posteroanterior Chest X-rays  | Completed               | COVID-19                                        | Device: CovX                                                                  | • The University of Ottawa Heart Institute, Ottawa, Ontario, Canada         |
| 50  | Rapid, Onsite COVID-19 Detection                                     | Enrolling by invitation | COVID-19                                        | Device: Rapid Onsite COVID-19 detection                                         | • University of Wisconsin, Madison, WI, USA                                 |
| 51  | Safety and Efficacy Of Hydroxychloroquine for At Risk Population (SHARP) Against COVID-19 | Not yet recruiting      | Coronavirus infection Hydroxychloroquine adverse reaction | Drug: hydroxychloroquine sulfate 200 mg (mg) tab                              | • Richmond Pharmacology Ltd. 1a Newcomen St, London Bridge, London, UK      |
| 52  | Validation of COVID-19 Tests                                         | Active, not recruiting  | COVID-19                                        | Diagnostic test: Covid-19 Rapid Test Kit (RAPG-COV-019)                                 | • Incor - Heart Institute - University of Sao Paulo, Sao Paulo, Brazil     |
| 53  | Pulmonary Optical Coherence Tomography in COVID-19 Patients          | Recruiting              | COVID-19                                        | Diagnostic test: quantitative IgG test                                          |                                                                           |
| No. | Title                                                                 | Status               | Conditions                                         | Interventions                                                                 | Locations                                                                 |
|-----|----------------------------------------------------------------------|----------------------|----------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 54  | COVID-19 Surveillance Based on Smart Wearable Device                  | Not yet recruiting   | COVID-19                                           |                                                                               | • IRCCS San Raffaele, Milano, Italy                                       |
|     |                                                                      |                      |                                                    |                                                                               | • Peking University First Hospital, Beijing, Beijing, China                  |
| 55  | Descriptive and Retrospective Analysis of Acute Myocarditis Associated with Pandemic COVID-19 in Children | Not yet recruiting   | COVID-19                                           |                                                                               | • Hôpital Bicêtre, Le Kremlin-Bicêtre, France                              |
|     |                                                                      |                      |                                                    |                                                                               | • Hôpital Armand Trousseau, Paris, France                                    |
|     |                                                                      |                      |                                                    |                                                                               | • Hôpital Necker-Enfants Malades, Paris, France                              |
|     |                                                                      |                      |                                                    |                                                                               | • Hôpital Robert Debré, Paris, France                                       |
| 56  | Diagnostic Value of New COVID-19 Antibodies Testing Among Laboratory Healthcare Workers | Not yet recruiting   | COVID-19                                           | Diagnostic test: COVID-19 antibodies testing                                 |                                                                               |
| 57  | A Clinical Trial of Mycobacterium w in Critically Ill COVID 19 Patients | Recruiting           | COVID-19                                           | Drug: suspension of heat killed (autoclaved) Mycobacterium w Drug: standard therapy of COVID-19 | • All India Institute of Medical Science, Raipur, Chhattisgarh, India       |
|     |                                                                      |                      |                                                    |                                                                               | • All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India    |
|     |                                                                      |                      |                                                    |                                                                               | • Postgraduate Institute of Medical Education and Research, Chandigarh, India|
|     |                                                                      |                      |                                                    |                                                                               | • All India Institute of Medical Science, Delhi, India                      |
| 58  | Convalescent Plasma In ICU Patients With COVID-19-Induced Respiratory Failure | Recruiting           | COVID-19 SARS-CoV-2                                 | Biological: multiple doses of anti-SARS-CoV-2 convalescent plasma             | • 8700 Beverly Blvd., Los Angeles, CA, USA                                 |
|     |                                                                      |                      |                                                    |                                                                               | • Johns Hopkins University, Baltimore, MD, USA                               |
| 59  | Immunoglobulin G Antibody Immune Response Profile Following Infection with SARS-CoV-2 in COVID-19 Egyptian Patients | Recruiting           | COVID-19                                           |                                                                               | • Sohag University Hospital, Sohag, Egypt                                  |
| 60  | Efficacy and Safety of Early COVID-19 Convalescent Plasma in Patients Admitted for COVID-19 Infection | Recruiting           | Severe acute respiratory syndrome coronavirus 2    | Biological: COVID-19 convalescent plasma                                       | • Hospital Clinico Universidad Católica, Santiago, Chile                    |
| 61  | Will Hydroxychloroquine Impede or Prevent COVID-19                   | Recruiting           | COVID-19 SARS-CoV-2                                 | Drug: Hydroxychloroquine—daily dosing Drug: hydroxychloroquine—weekly dosing Other: placebo oral tablet Diagnostic test: monitoring visit—baseline Diagnostic test: monitoring visit—week 4 Diagnostic test: monitoring visit—week 8 Other: weekly assessment | • Henry Ford Hospital, Detroit, MI, USA                                    |
|     |                                                                      |                      |                                                    |                                                                               | • Detroit Department of Transportation (DDOT), Detroit, MI, USA              |
|     |                                                                      |                      |                                                    |                                                                               | • Detroit Fire Department & Detroit EMS, Detroit, MI, USA                  |
|     |                                                                      |                      |                                                    |                                                                               | • Detroit Police Department, Detroit, MI, USA                               |
| 62  | Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID-19: a Randomized Control Trial | Not yet recruiting   | SARS-CoV-2 infections COVID-19                     | Drug: oral                                                                   | • Assistant Professor Subsai Kongsuangdao, Bangkok, Thailand               |
| 63  | Recruiting                                                          | COVID-19             |                                                    |                                                                               | • Louis Mourier hospital (AP-HP), Colombes, France                          |
| No. | Title                                                                 | Status                      | Conditions                                                                 | Interventions                                                                                                    | Locations                                                                 |
|-----|----------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 64  | Predicting the Need for Intubation in Hospitalised COVID-19 Patients (PRED ICU COVID19) | Recruiting                  | Coronavirus infection Intensive care patients                             | Other: data monitoring for 48 h within the first 12 h of admission for COVID-19                                | • Brabois Hospital (CHRU de Nancy), Vandevaux-lès-Nancy, France          |
| 65  | Effects on the Qt Interval of COVID-19 Coronavirus Infection          | Recruiting                  | COVID-19                                                                  | Biological: COVID-19 convalescent plasma                                                                       | • Hospital of the University of Pennsylvania, Philadelphia, PA, USA       |
| 66  | COVID-19 Pandemic and Worldwide Organ Procurement                    | Recruiting                  | COVID-19                                                                  | Diagnostic test: COVID-19 swab PCR test                                                                      | • Paris Transplant Group, Paris, France                                  |
| 67  | Testing the Accuracy of a Digital Test to Diagnose Covid-19          | Recruiting                  | COVID-19                                                                  | Other: observation                                                                                           | • King’s College London, London, United Kingdom                           |
| 68  | Clinical Trial of Allogeneic Mesenchymal Cells from Umbilical Cord Tissue in Patients with COVID-19 | Recruiting                  | COVID                                                                     | Biological: mesenchymal cells Drug: standard of care                                                        | • Hospital Universitario de Getafe, Getafe, Madrid, Spain                |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital Universitario de Cruces, Barakaldo, Spain                                                               |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital Universitario de La Princesa, Madrid, Spain                                                             |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital Infantil Universitario Niño Jesus, Madrid, Spain                                                        |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital Ramón Y Cajal, Madrid, Spain                                                                              |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Complejo Universitario La Paz, Madrid, Spain                                                                    |
| 69  | The Heart Hive COVID-19 Study                                       | Not yet recruiting          | COVID-19 Cardiomyopathies                                                 | Other: COVID-19 experience surveys                                                                            | • Imperial College London, London, UK                                   |
| 70  | National Survey of Symptoms of People Aged 70 and Overs Diagnosed with COVID-19 | Completed                  | SARS-CoV-2 COVID-19                                                        | Other: observation                                                                                           | • Angers University Hospital, Angers, France                           |
| 71  | Seroconversion Among Staff at a Large Acute Care Hospital in Denmark During the COVID-19 Pandemic | Recruiting                  | COVID-19 Health personnel Personnel, hospital                            | Other: serial seroconversion measurements in hospital employees during the COVID-19 pandemic                  | • Nordsjællands Hospital, Hillerød, Capital Region, Denmark            |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Nykøbing Falster County Hospital, Nykøbing Falster, Southern Region, Denmark                                   |
| 72  | Clinical Trial of Efficacy and Safety of Sinovac’s Adsorbed COVID-19 (Inactivated) Vaccine in Healthcare Professionals | Not yet recruiting          | COVID-19                                                                  | Biological: adsorbed COVID-19 (inactivated) vaccine Biological: placebo                                        | • Universidade de Brasilia, Brasilia, DF, Brazil                        |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil                                                  |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital das Clínicas da Universidade Federal do Paraná, Curitiba, PR, Brazil                                 |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil           |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital das Clínicas da UNICAMP, Campinas, SP, Brazil                                                         |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil |
|     |                                                                      |                             |                                                                           |                                                                                                               | • Instituto de Infectologia Emilio Ribas, Sao Paulo, SP, Brazil                                                      |
| No. | Title                                                                 | Status                  | Conditions | Interventions                                    | Locations                                                                 |
|-----|----------------------------------------------------------------------|-------------------------|------------|-------------------------------------------------|---------------------------------------------------------------------------|
| 73  | Gut Microbiota, “Spark and Flame” of COVID-19 Disease                | Recruiting              | COVID-19   | Other: exposure                                 | • Centro de Pesquisas Clínicas do Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, SP, Brazil  
  • Instituto Israelita de Ensino e Pesquisa Albert Einstein, Sao Paulo, SP, Brazil  
  • Universidade Municipal de São Caetano do Sul, São Caetano do Sul, SP, Brazil  
  • Faculdade de Medicina de São José do Rio Preto - FAMERP, São José Do Rio Preto, São Paulo, Brazil  
  • Instituto de Infectologia Evandro Chagas - Fiocruz, Rio De Janeiro, Brazil |
| 74  | Antioxidant Therapy for COVID-19 Study                               | Not yet recruiting      | COVID-19   | Dietary supplement: antioxidation therapy  
  Other: standard of care                                                  | • Hospital CUF Infante Santo, S.A., Lisbon, Portugal  
  • Hospital de São Francisco Xavier, Lisbon, Portugal  
  • Centro Hospitalar Universitário São João, Oporto, Portugal  
  • Abia State Isolation Centre, Amachara, Umuahia, Abia State, Nigeria  
  • Benue State University Teaching Hospital, Makurdi, Benue State, Nigeria  
  • Brigadier Abba Kyari Memorial Hospital, Borno, Borno State, Nigeria  
  • University of Maiduguri Teaching Hospital, Maiduguri, Borno State, Nigeria  
  • University of Calabar Teaching Hospital, Calabar, Cross River, Nigeria  
  • Federal Medical Centre Idi-Aba, Abeokuta, Ogun State, Nigeria  
  • Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria  
  • Infectious Disease Hospital, Amanawa, Sokoto State, Nigeria  
  • Murtala Muhammad Specialist Hospital, Sokoto, Sokoto State, Nigeria  
  • Occupational Therapy Center, Sokoto, Sokoto State, Nigeria  
  • Usmanu Danfodiyo University Teaching Hospital, Sokoto, Sokoto State, Nigeria  
  • AO San Paolo, Milan, IT, Italy |
| No. | Title                                                                 | Status       | Conditions                                                                 | Interventions                                      | Locations                                                        |
|-----|----------------------------------------------------------------------|--------------|----------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------|
| 76  | Polymorphisms in Patients (COST ACTION)                               | Completed    | COVID-19                                                                   | Diagnostic test: COVID-19 diagnostic PCR           | Seda Yılmaz Semerci, Istanbul, Turkey                           |
| 77  | Inhaled Nitric Oxide for Preventing Progression in COVID-19 Pandemic  | Recruiting   | COVID-19                                                                   | Drug: nitric oxide                                | Tufts Medical Center, Boston, MA, USA                           |
| 78  | Cohort of Patients Infected with SARS-CoV2 (COVID-19) or Suspected of Being | Recruiting   | COVID-19                                                                   | Other: blood samples                              | GH Pitié-Salpêtrière / Service d’Accueil des Urgences, Paris, Ile-de-France, France |
| 79  | Hydrogen-Oxygen Generator with Nebulizer in the Improvement of Symptoms in Patients Infected with COVID-19 | Recruiting   | COVID-19                                                                   | Device: oxyhydrogen Device: oxygen               | First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China |
| 80  | Endovascular Thrombectomy in COVID-19 Infected Patients              | Completed    | Ischemic stroke                                                            | Other: mechanical thrombectomy                    | UH Montpellier, Montpellier, France                             |
| 81  | Pre-exposure Prophylaxis with Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic | Suspended    | COVID-19                                                                   | Drug: hydroxychloroquine Drug: placebos           | ISGlobal, Barcelona, Spain                                     |
| 82  | Evaluating Clinical Parameters of COVID-19 in Pregnancy               | Not yet recruiting | 2019 novel coronavirus infection COVID-19 infection | Other: COVID-19 positive via testing             | Chelsea and Westminster Hospital NHS Foundation Trust, London, UK |
| 83  | Characteristics of COVID-19 Infection Among PREGnant Women           | Recruiting   | Coronavirus infection COVID-19 related                                     | Other: COVID-19 positive via testing             | INOVA Health System, Falls Church, VA, USA                     |
| 84  | Combination of Chest Scanography and Nasal Viral Detection Test to Detect COVID-19 Positive Patients Before Surgical Intervention in a University Hospital During Coronavirus Pandemic | Active, not recruiting | COVID-19, SARS-CoV-2                                                      | Other: physiotherapy                                            | UH Montpellier, Montpellier, France                             |
| 85  | Implementation of Physiotherapy on COVID-19 Patients in ICU          | Recruiting   | SARS-CoV-2, COVID-19                                                        | Other: mechanical physiotherapy                   | UH Montpellier, Montpellier, France                             |
| 86  | Tableted COVID-19 Therapeutic Vaccine                                | Active, not recruiting | COVID-19                                                                  | Biological: V-SARS                                   | Immunitor Inc., Vancouver, BC - British Columbia, Canada       |
| 87  | Effects of COVID-19 Convalescent Plasma (CCP) on Coronavirus-Associated Complications in Hospitalized Patients | Recruiting   | COVID-19, SARS-CoV-2                                                        | Biological: COVID-19 convalescent plasma CCP      | UCSF Medical Center at Mount Zion, San Francisco, CA, USA       |
| 88  | Kerecis Oral and Nasal Spray for Treating the Symptoms of COVID-19   | Recruiting   | COVID-19                                                                   | Device: Kerecis oral and nasal spray Other: placebo | National Hospital of Iceland (Landsditali), Reykjavik, Iceland   |
| 89  | Anti COVID-19 Convalescent Plasma Therapy                            | Not yet recruiting | COVID-19                                                                  | Biological: anti-SARS-CoV-2 convalescent plasma    | Red de Investigacion Vascular (SEACV), Madrid, Spain             |
| 90  | Influence of COVID-19 Infection in Thromboembolic Venous Disease: National Cohort Study | Not yet recruiting | COVID-19                                                                  | Other: deep venous disease diagnostic              | University of California, San Francisco Medical Center (Parnassus Campus), San Francisco, CA, USA |
| 91  | Elmo Respiratory Support Project - COVID-19                           | Not yet recruiting | COVID-19                                                                  | Other: Elmo Project at COVID-19: study in humans   | University of California, San Francisco Medical Center (Parnassus Campus), San Francisco, CA, USA |

Table 1 (continued)
COVID-19 patients, including plasma therapy. Recently, convalescence plasma therapy in which the immunoglobulin of cured COVID-19 patients is injected into a severe patient as a treatment option is explored in India, China, and the USA. Table 1 shows the status of recent clinical trials of vaccines against SARS-CoV-2 infection. Table 2 shows the current status of the clinical trials of vaccines and candidate therapy for cytokine release syndrome (CRS) against SARS-CoV-2 infection.

**Table 1 (continued)**

| No. | Title | Status | Conditions | Interventions | Locations |
|-----|-------|--------|------------|---------------|-----------|
| 92  | Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia | Recruiting | COVID-19 pneumonia | Device: Elmo Project at COVID-19: proof of concept and usability | • Centenario Hospital Miguel Hidalgo, Aguascalientes, Mexico |
|     |       |        |            | Drug: plasma from COVID-19 convalescent patient | |
|     |       |        |            | Drug: human immunoglobulin | |
| 93  | Observational Cohort of COVID-19 Patients at Raymond- Poincare | Recruiting | COVID-19 | Device: Q-NRG Metabolic Cart Device | • Department of Infectiology, Raymond Poincaré Hospital, APHP, Garches, France |
|     |       |        |            | Device: MuscleSound Ultrasound | |
|     |       |        |            | Device: multifequency bioimpedance spectroscopy | |
| 94  | Longitudinal Energy Expenditure and Metabolic Effects in Patients with COVID-19 (LEEP-COVID) | Recruiting | COVID-19 | Biological: SARS-CoV-2 specific T cells | • Duke University Medial Center, Durham, NC, USA |
| 95  | Part Two of Novel Adoptive Cellular Therapy with SARS-CoV-2 Specific T Cells in Patients with Severe COVID-19 | Recruiting | COVID-19 | Biological: anti-SARS-CoV-2 convalescent plasma | • Changi General Hospital, Singapore, Singapore |
|     |       |        |            | Biological: SARS-CoV-2 specific T cells | • KK Women’s and Children’s Hospital, Singapore, Singapore |
|     |       |        |            | Biological: SARS-CoV-2 specific T cells | • National University Hospital, Singapore, Singapore |
|     |       |        |            | Biological: SARS-CoV-2 specific T cells | • Sengkang General Hospital, Singapore, Singapore |
|     |       |        |            | Biological: SARS-CoV-2 specific T cells | • Singapore General Hospital, Singapore, Singapore |
|     |       |        |            | Biological: SARS-CoV-2 convalescent plasma | |
| 96  | A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients with COVID-19 Infection | Recruiting | COVID-19 | Biological: anti-SARS-CoV-2 convalescent plasma | • Froedtert Hospital, Milwaukee, WI, USA |
| 97  | Identification of Predictors for the Evolution of COVID-19 Related Pneumonia by Transcriptomic and Seroproteomic | Recruiting | COVID-19 interstitial pneumonia | Diagnostic test: lung ultrasound | • IRCCS Policlinico San Donato, San Donato Milanese, MI, Italy |
| 98  | CORonavirus (COVID-19) Diagnostic Lung UltraSound Study | Not yet recruiting | COVID-19 | Biological: SARS-CoV-2 convalescent plasma | • LifeFactors Zona Franca SAS, Medellin, Antioquia, Colombia |
| 99  | Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19 | Not yet recruiting | Coronavirus disease 2019 (COVID-19) | Biological: COVID-19 convalescent plasma | |
|     |       |        |            | Biological: anti-COVID-19 human immunoglobulin | |
|     |       |        |            | Drug: standard (specific) therapy for COVID-19 | |
|     |       |        |            | Drug: tramadol | |
|     |       |        |            | Other: standard care delivered in the isolation hospitals | |

**Immune Catastrophe in the Panic of Self-Defense**

The immune response is a strong defense against invasive pathogens. Recent studies demonstrated an acute inflammation in the severely affected COVID-19 patients, leading to cytokine storm, acute respiratory distress, and then multiple organ failure. Nutritional interventions including vitamin C and D and antioxidants are also used to boost the immune
response against this disease. After the recent demonstration of the crystal structure of spikes in SARS-CoV-2 [64], several opportunities had emerged for the development of a vaccine for COVID-19 treatment. The S protein in the spike of SARS-CoV-2 is the major target for vaccine development, and several companies are now in the advancing stage of an effective therapeutic strategy against SARS-CoV-2. Figure 3 shows the proposed treatment strategies targeting ACE2 receptors and the receptor-binding domain (RBD) of the spike for designing a promising drug therapy against COVID-19.

Proposed Hypothesis

We propose a “Pitchfork self-defense hypothesis” where a varied and wide range of effects are observed among the infected population from mild symptoms to multiorgan failure leading to death. This all is owing to the flawed genome and incompetent immune system which acts as a rod for its own back in the rage of self-defense. The peculiar aspect is the reckless and speedy multiplication of virus resulting in the accumulation of monstrous viral copies which in turn calls for a “save the ship” signal activation. The defense system, sensing this as a hulking danger, apparently must be reacting in an exaggerated manner, deploying and marching its armed forces to the site of infection in the form of the cytokine storm syndrome. This storm would do more harm than good, engulfing the healthy RBCs and WBCs, and further inviting more of the type to the site of infection. Thus, this likely stimulates the blood vessels to leak out the immune cells in adjoining tissues, pouring fluid into the lungs. This pneumonia-like condition undoubtedly must be activating cell suicide in lung tissue and hence tearing off the alveoli. Air sacs failing to exchange gases would lead to chronic oxygen starvation which finally culminates in respiratory distress. Thus, in almost 100% of cases, the first critical clinical sign is respiratory unrest which fits in the said hypothesis perfectly. Once the blood vessels lose their fluid, a sudden drop in blood

| Company                      | Approach          | Stage          | Strategy                                      |
|------------------------------|-------------------|----------------|-----------------------------------------------|
| Arcturus Therapeutics        | Vaccine           | Phase 1/2      | Engineering RNA with nanoparticle mRNA        |
| BioNTech                     | Vaccine           | Phase 3        | RNA recombinant measles virus                 |
| Zydus Cadila                 | ZyCoV-D vaccine   | Phase 1/2      | Live attenuated virus                         |
| Mudoch Children’s Research Institute | BCG vaccine     | Phase 2/3      | Virus-like particle                           |
| Medigaco, GSK, Dynavax       | Plant-based vaccine | Phase 1      | Man-made mRNA                                 |
| CureVac                      | Vaccine           | Phase 1        | Engineering adjuvants with proteins           |
| Eli Lilly                    | Treatment         | Phase 3        | DNA vaccine                                   |
| GlaxoSmithKline+ Clover Biopharmaceuticals | Vaccine | Phase 1      | Deactivated virus                             |
| Inovio Pharmaceuticals       | Vaccine and treatment | Phase 1/2 | Has not yet revealed strategy, five-point plan released RNA vaccine |
| Johnson & Johnson            | Vaccine and treatment | Phase 1/2 | Cocktail of antibodies                        |
| Pfizer-BioNTech              | Vaccine and treatment | Phase 2/3 | Chimera of RNA viruses, Kevzara drug          |
| Regeneron Pharmaceuticals    | Treatment         | Phase 3        | Plasma of treated patients                    |
| Sanofi                       | Vaccine and treatment | Phase 3 | Viral replication inhibitor                   |
| Takeda                       | Treatment         | Treatment phase | Cocktail of danoprevir and titonavir        |
| Vir Biotechnology            | Treatment         | Phase 1        | Isolated strain                               |
| Ascleitis Pharma             | Treatment         | Phase 1b       | Using a platform first developed for Ebola    |
| Gamaleya Institute of Epidemiology and Microbiology | Vaccine | Phase 2 | RNA vaccine (mRNA -1273)                      |
| Siberian Vector Institute    | Vaccine           | Phase 1        | SARS-CoV-2 genetic code                       |
| Moderna Therapeutics         | Vaccine           | Phase 3        |                                              |
| CanSino Biologics            | To start phase 3  |               |                                              |

Table 2 (continued)

| Company                      | Approach          | Stage          | Strategy                                      |
|------------------------------|-------------------|----------------|-----------------------------------------------|
| Gilead Sciences              | Treatment         | Phase 3        | Remdesivir                                    |
| Oxford University            | Vaccine           | Phase 2/3 trial in UK, phase 3 trials in SA and Brazil | AZD 1222 Non-replicating virus |
| Bharat Biotech               | Vaccine           | Phase 1/2      | COVAXIN inactivated virus                     |

Table 2 Current status of the clinical trials of vaccines and candidate therapy for cytokine release syndrome (CRS) against SARS-CoV-2 infection (Source: National Institute of Health, https://clinicaltrials.gov/) Accessed on Aug 1, 2020
Pressure is observed. This may probably be causing clogging of blood vessels and clotting of blood in several tissues leading to a shortage of blood supply and oxygen to the vital organs. This expectedly would have a shocking climax of multiple organ failure. But, interestingly, not all individuals meet with the same fate. Moreover, there are different categories into which individuals can be divided into, as follows: (1) extremely vulnerable category which includes people with an impaired immune system, a chronic respiratory condition, cancer, etc. who cannot afford a competent immune response and are sure to succumb to the disease; (2) high-risk category which includes old people, pregnant women, obese people, and diabetic patients, who are highly susceptible owing to low immunity; and (3) low-risk category which includes healthy and younger individuals who are well equipped to give a tough fight. Frontline workers (mainly doctors, workers, and police personnel) remain in the high-exposure zone and so have a greater chance of contacting COVID-19. Unreasonable and hectic service schedules make the fall prey to the virus since a tired and restless body temporarily loses on its immunity. But there are also reports where young, healthy, and shielded individuals were victimized to death due to COVID-19. The abnormal immune system rests on a faulty genome; thus, the strongest are selected and the defective perish. This can be explained with the present hypothesis in the sense that some immune defects remain latent and are expressed only when a virus triggers them. In the first few days of catching any infection majorly, natural killer cells and macrophages take charge in containing the pathogen and preventing against any severe damage in the body. In case these fail to fight out the infection, then B and T lymphocytes come in the picture and rage a stronger defense response [65]. People with impaired immune systems are more vulnerable to severe infections. Many evidences support this view. (1) One of the most buttressing exemplar is that patients having impaired perforins (perforinopathies) tend to trigger a very severe cytokine storm. These perforins are stocked in natural killer cells and cytotoxic T lymphocytes. Since perforins are glycoproteins that are critically responsible for pore formation in the host cell (infected with virus) causing immune cell-mediated death of the target cell, thus, reduced attenuated expression of perforins invites a cytokine storm. Thus, if such patients are provided with sufficient amounts of perforin, then it may help generate a healthy immune response against SARS-CoV-2 infection. (2) Also IL-6 blocks the expression of granzyme B and perforins and prevents the killing of the viral-infected cell (experimentation studies on mice). Therefore, it is of concern to note that in COVID-19 patients succumbing to heart attack, IL-6 prevented the activity of STAT-5 signal transducer, thereby decreasing perforin levels. Thus, a treatment involving anti IL-6R would be quite effective against COVID-19 infection. In a nutshell, patients with weakened immune systems tend to show severe symptoms because of elevated levels of IL-6 mediated by poor perforin functionality [66]. It has been discovered by the Indo-US research team that the Indian population is better equipped with these killer cell immunoglobulin-like receptor genes (KIR genes) and therefore can contain the infection in the initial
stage itself. Thus, Indian populations are less susceptible to these infections and also confer Indians with stronger immunity against other viruses, autoimmune diseases, and even tumors [67]. However, recently, this claim was opposed and declared baseless by a few science researchers and science magazine editors [68]. Thus, the answer lies in developing artificial adaptive immunity through an effective medicine.

**Genome Analysis/Genomics Could Help Resolve Some Unanswered Questions** A comprehensive genome analysis of the virus as well as the host population to predict genetic determinants is the need of the hour. Such a large-scale collaborative task of genome sequencing may unmask hidden mysteries like severity and susceptibility of COVID-19. Many such initiatives using high-throughput sequencing technologies are in the pipeline (namely Genomics England, UK Biobank). Since we know that genome is unique to an individual and it is the sole dower of phenotypic or functional expression of a trait, so it is imperative to first analyze the defect at the molecular level. This would open a gamut of doors for therapeutic and preventive strategies and may help answer all the puzzles concerning COVID-19. Once we know the gene, we may easily correlate any defect in its protein expression and biochemical pathway concerning the disease. This gene structure would also give an insight into new and ameliorating drugs and therapies.

**Current Therapeutic Strategies for the Development of an Effective Vaccine Against COVID-19**

In this hour of COVID-19 pandemic, a population of 7.8 billion can be safeguarded only by active immunity. Natural active immunity cannot be expected from the diseased chunk of the population supporting a fragile immune system. Also, isolation alone cannot help, since it is not an indelible solution. Thus, developing an effective vaccine is utmost required to develop adaptive immunity to fight upcoming viral infections. Thus, today, countries vie with each other for developing an effective vaccine against SARS-CoV-2. To date, approximately 100 designs of different vaccines have been proposed worldwide and more than six groups of these vaccines have already undergone trial (Fig. 4).

**Angiotensin-Converting Enzyme-2 (ACE-2) Receptor-Viral Doorknob-Based Therapy** Dozens of pharmaceutical companies are targeting this key to unlock a SARS-CoV-2 vaccine. Different strategies are being worked upon. It was recently discovered that ACE receptors are present not only on lung, heart, gut, and kidney cells but also on the nose. Using ACE receptors in therapeutics holds a contrasting version. Some research teams undermine its potentials citing that non-steroidal inflammatory drugs may spoil the show by increasing the expression of ACE receptors, while others emphasize that using a floating enzyme strategy may prove effective. These ACE receptor mimics may befool viruses and make them latch on (Apeiron Biologics, an Austrian pharmaceutical company). We propose that a gene variation study of the ACE-2 gene specific to lung tissue can be instrumental in discovering effective drugs against viral entry since this gene deals with the production of surfactant for the lungs. Any defect or overexpression of this gene may either prevent viral entry into the host cell or may make it detrimental for the host. One such research to support our proposal is the CCR5 gene on blood cells. Genetic analysis revealed that people with defective CCR5 gene prevented HIV from entering the host cell [69]. Thus, in this case, a defective gene was at an advantage since it made some people immune to HIV infection by preventing viral entry. One of the observed trends in COVID-19 is the cytokine storm (similar to the one observed in H1N1 flu). This also results from some impaired gene which causes a hyperexpressive immune response. Thus, a genetic variation study among populations would help figure out who is less vulnerable and who is more prone to such deadly viruses. The viral genomics and proteomics studies would help to discover some relevant transcription factors that induce overexpression of the host immune system. In a recent proteomics study of SARS-CoV-2-infected host cells, a fresh understanding of some gene therapies effective against COVID-19 was hinted. It includes the modulations in the host cell pathway infected with SARS-CoV-2 in human cell culture studies and suggests that effective therapy can be blocking these pathways by some inhibitor molecules that would halt the process of viral multiplication.

**MicroRNA, a Direct Attack on the Viral Genome** The miRNAs are small, non-coding, single-stranded RNA molecules, which are known to modulate a variety of vital physiological processes including RNA silencing, post-transcriptional regulators of gene expression involved in cardiovascular development and health [70–75]. Several thousand human genes, amounting to about one third of the whole genome, are potential targets for regulation by the several hundred miRNAs encoded in the genome [76]. It is evident from the previous studies that novel miRNAs can be used as promising tools as diagnostic biomarkers and therapeutic drug targets for several diseases [77–79]. In the present context, microRNAs specifically mitochondrial microRNA can prove as a panacea. Silico analysis studies have been used to interpret which host microRNAs have complete complementarity with viral RNA so that viral RNA expression can be silenced.

Recently, microRNA-5197-3p has been identified as the most valuable site for interaction with SARS-CoV-2, and complete complementary miRNA regions in the viral genome have been predicted. This proposed site lacks any side effect
or competition and a synthetic microRNA constructed based on this template may act as a remarkable candidate for the treatment of COVID-19. These may then be packed into exosomes and either injected into the blood for multiple organ treatment or simply inhaled into the lungs through nebulizers. Antiviral miRNAs present in the host target specific genes of the virus and interfere with viral molecular processes vital for reproduction, namely replication, protein synthesis, and phenotypic expression. Thus, microRNAs are vital tools for tailoring and silencing viral genome as these complementarily bind to the viral genome and prevent their expression. It has been found that hsa-miR-27b is uniquely specific to only SARS-CoV-2 found in India, and so, Indian populations are naturally endowed with a miraculous antidote to this virus. Alnylam and Vir, two big companies, are working on temporarily silencing the ACE2 receptors using interference RNA technology. They believe that when there will be no receptors, then viruses would not be able to enter. But another big challenge is delivering these RNA molecules to the target site. It has been proposed that these microRNA would probably be packed in fat vesicles and inhaled in the form of a dry powder. But most researchers are skeptical about this as knocking down these vital blood pressure-regulating receptors may prove fatal. To speed up the emergency medical need of vaccines and therapies against COVID-19, the Food and Drug Administration (FDA) of the USA has provided fast-track designation to Mrna Vaccine mRNA-1273 created by Moderna. It is in phase II of the clinical trial. Moderna is highly trusted as earlier it could fast-track the Zika vaccine.

Recombinant Vaccine It is a recombinant adenovirus vaccine developed by the University of Oxford. ChAdOx1 nCoV-19 has been genetically engineered using weakened common cold adenovirus (ChAdOx1) infective only to chimpanzees. Genes coding for spike glycoprotein (S) of SARS-CoV-2 virus have been inserted into these viruses as these spike
proteins are vital to bind on to ACE2 receptors on human cells. Its peculiar feature is that MenACWY has been used as an active control instead of saline solution. It gave very encouraging positive results on monkeys, generating antibodies within 28 days of its administration. It also drastically reduced respiratory distress in the patients and also prevented viral replication. Its human trials are in the process, and the university has already signed an agreement for its global manufacture and sale with Astra Zeneca. It is under trial on humans and is estimated that the initial study would include more than 1100 healthy subjects between 18 and 55 years of age. Exclusion criteria include pregnant, breastfeeding mothers and COVID-19 patients.

Epitope-Based Vaccines The coronavirus has spike proteins on its shell which are essential to latch on to the host cellular receptors. Viruses have been smart enough to evade the host’s defense system by hiding their receptor binding motif (RBM). Thus, one of the strategies could be to design a vaccine targeting the RBM of SARS-CoV-2 virus. Tel Aviv University (TAU) of Israel is working on the same plan in association with Neovii, a pharmaceutical company. They aim to come up with a COVID-19 epitope vaccine based on in silico or computational prediction. It will be a cost-effective solution with great therapeutic efficacy.

Drug Against Cytokine Storm The National Institutes of Health (NIH), USA, has sponsored a biotechnology company, CytoAgents, to fast-track the production of GP1681. This would be effective in controlling the cytokine storm resulting from the SARS-CoV-2 infection. These are small molecules known to show a host-directed methodology to spot the fundamental reason of cytokine storm, altering the host’s natural immune system. This molecule would be effective against other viral diseases like influenza. It is currently under phase I and II of the human trial.

There are enough case studies that have reported an exaggerated and abnormal production of IL-6 that led to “cytokine storm” and which finally ended up in heart failure due to stimulation of the coagulation process. Also, tissue necrosis and infiltration of monocytes and macrophages are commonly observed in both COVID-19 patients showing severe symptoms and postmortem pathological analysis. The authors propose that there is a good possibility that anti-interleukin-6 (IL-6) therapy may manage COVID-19-induced cytokine storm (hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and sepsis) [80]. Cytokines IL-6, IL-2, IL-1β, IL-8, IL-17, IL-10, and IL-4 all have known to increase excessively during COVID-19. Tocilizumab is a human monoclonal anti-IL-6 receptor antibody, extracted from patients with cytokine release syndrome. This is in phase 4 for SARS-CoV-2 trial. Tocilizumab can be associated with soluble IL-6R and mIL-6R, and inhibit signal transduction. However, it is a very costly treatment and its safety risks need to be tested in clinical trials [80-82].

Adjuvant Vaccine for COVID-19 Adjuvant is generally a chemical/drug or immunological agent added to a vaccine in small amounts to increase the production of antibodies. Thus, an adjuvant vaccine would probably provide instant and long-lasting immunity. GlaxoSmithKline and Sanofi Pasteur (French Pharma-Company) together are working on the development of an adjuvant vaccine against SARS-CoV-2.

Synthetic Chimeric COVID-19 Vaccine Reconstruction of live synthetic less virulent SARS-CoV-2 virus which may provide vaccine protection against COVID-19 is in the pipeline. This commendable project is being taken up by Tonix Pharmaceuticals which had earlier developed the horsepox virus vaccine on a similar plan. University of Alberta, Canada, has signed a licensing agreement with Tonix Pharmaceuticals. Their basic plan is to synthesize some antigen genes of SARS-CoV-2 to innervate T cell immune response. They have a license to create 3 vaccines for COVID-19, namely TNX-1810, TNX-1820, and TNX-1830. Currently, it is at the pre-investigation of new drug stage. This kind of vaccine no doubt can prove miraculous but at the same time may instigate certain criminal minds to construct deadly bioweapons.

Emetine Injections National Center for Advancing Translational Sciences (NCATS) and Acer Therapeutics (pharmaceutical company) have agreed on placebo-controlled and random tests of this antiviral drug on COVID-19 patients.

NVX-CoV2373 Vaccine The Coalition for Epidemic Preparedness Innovations (CEPI) has agreed to fund $384m to Novavax for manufacturing Matrix-M adjuvant and NVX-CoV2373 vaccine antigen of COVID-19 vaccine which would boost rapid production of antibodies.

Antibody Cocktail COVI-SHIELD Some researchers at Mount Sinai Health System have come up with the idea of developing a triple-antibody prophylactic and therapy. This antibody cocktail specifically would safeguard frontline workers and doctors who are frequently exposed to this virus. They aim at screening approximately 1500 COVID-19 recovered patients for identifying and isolating at least 3 vital antibodies against spike proteins of SARS-CoV-2 virus from their blood plasma. Then, monoclonal antibodies would be synthesized in collaboration with Sorrento Therapeutics. This would specifically provide immunity to the high-risk population for at least 2 months. This therapy may also provide resistance to future virus mutations and is currently filing an Investigational New Drug (IND) application.

Novel Decoy Cellular Vaccine Transgenic antigen-expressing cells: In this innovative strategy, nonreplicating, irradiated cells
dead viruses as are live and draw out a strong immune response. But these vaccines provide only short-term immunity and their booster doses are required. Such weakened viruses are actual viruses with some mutations that make them more attracted to other animals than humans. Such viruses are created by culturing them in tissues of some other animal. Thus, a mutant form of the virus is chosen that would prefer other non-human animal hosts and would hardly infect humans. Vaccines made from such weakened viruses when injected into humans may provide immunity against viruses and at the same time avoid exaggerated infection. Thus, such vaccines usually show mild side effects post-treatment. Some of the examples are rotavirus, measles, mumps, rubella (MMR combined vaccine), smallpox, etc. Thus, both live and attenuated vaccines train our body to fight against infection as they are more natural. Some of the limitations of such vaccines include refrigeration to keep them alive; costly instrumentation to protect them from any new virulent mutation (or reversion) during transportation to distant places; reliability deficit in the effectiveness of the vaccine and safety after administration.

Conjugate Vaccines Sometimes viruses have some modulating or disguising outer envelope proteins that have the capacity tobefool the host’s immune system by concealing their antigens. Thus, such viruses go unnoticed by the host defense system and invade different organs. Live or weakened vaccines generally do not work in such cases, and thus, conjugate or subunit vaccines are made by attaching a characteristic antigen from some other familiar pathogen on to the virulent virus’s coat. It works because the body’s immune system learns to recognize this masked virus as a potential threat in the light of a known pathogen, e.g., *Haemophilus influenzae* type B (Hib).

Nucleic Acid Vaccines In this approach, DNA from the virus is genetically engineered (with specific spike protein genes) and introduced into the host body as a plasmid, thus eliciting an immune response against those antigens. This probably remains harmless but, in turn, teaches the body to identify harmful viruses and produce antibodies against them. But this has never been tested on humans to date and is not yet licensed (20% of current vaccine research focuses on this approach).

Recombinant Vaccines Specific spike protein-producing gene segments are inserted into vectors (adenovirus) for vaccine delivery. Adenoviruses are good vectors for vaccine development because they can infect a wide range of hosts; cause effective expression of transgene; can be cultured in laboratories at low cost; do not allow lysogeny of viral genes into host genes; and can trigger an immune response by infecting dendritic cells and target both systemic and mucosal immune response. Johnson and Johnson, a US-based company, is working on this project (26% of current vaccine research focuses on this approach).
Virus-Like Particles (VLP) Specialized empty (without genetic material) lipid vesicles are prepared with spike proteins on the surface that mimic a true virus, and the body’s immune system reacts in response to this. These could serve as excellent vaccine candidates (33% of current vaccine research focuses on this approach).

Conclusions and Future Challenges

Worldwide, millions of people are infected, and thousands of deaths are occurring due to the pandemic situation of COVID-19. Unfortunately, no therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2. The identification of effective strategies against SARS-CoV-2 is a major challenge. Currently, we are fighting a twenty-first century disease with twentieth century weapons. The clinical trials of repurposing the existing antiviral agents against this potentially fatal disease are going on across the world. Recently, several possibilities including targeting viral binding receptors (ACE2) and spike proteins, stimulating an immune response, monoclonal antibodies, peptides, small-molecule drugs, etc. are being explored against emerging SARS-CoV-2 infection. However, the whole world is facing a challenge in dealing with a new coronavirus infection that has just emerged in humans and we are not having the existing vaccine or a drug against this potentially fatal disease. We hope that through these accelerated and determined plans, very soon, an effective vaccine that targets SARS-CoV-2 will be developed to settle this global COVID-19 issue. In closing, we express our concern about fading away from these big programs and funds offered to sort this public health crisis (generally offered around such pandemic). We would be witnessing many new and far deadlier viral pandemics in the ensuing time, and thus, we really need to be prepared to tackle this unseen danger. Thus, we need to continue this research with the same enthusiasm and zeal to discover reliable and affordable therapeutic strategies to curb such pandemics.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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