**REVIEW ARTICLE**

# Therapeutics and Vaccines: Strengthening Our Fight Against the Global Pandemic COVID-19

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## Abstract

The newly identified 2019 novel coronavirus (SARS-CoV-2) has become a public health concern globally posing a significant threat to human health and economy and creating an unprecedented crisis in all spheres of the global life. Emergence of new genotypes of SARS-CoV during the last few years has pointed out the limited efficacy of available vaccines and antivirals, constraining the global response to the COVID-19 outburst to largely monitoring/containment. There is high priority for treatment regimes and new potential therapeutic and vaccine strategies. Several candidates have shown promising outcomes in various in vitro and in vivo models. In addition, clinical trials are in progress to test conceivable therapies showing promising outcomes in various in vivo studies. Unfortunately, very little information is available in the scientific scope which offers details to the diverse strategies being targeted to fight the pandemic, particularly with respect to the molecular targets. This review article summarizes and highlights the ongoing advances and approaches that are being carried out across the globe in designing vaccines and novel therapeutics, with particular reference to the previous knowledge gained from other viral infections like with the earlier SARS and MERS-CoV. A detailed knowledge may pave the way to combat this pandemic COVID-19 as well as prevent similar deadly epidemics in future.

## Introduction

Coronaviruses (CoV) are positive-stranded RNA viruses that are responsible for a number of respiratory, gastrointestinal and neurological illnesses [1]. Over the past years, the world has witnessed the outbreak of two major pandemics SARS-CoV in 2003 and MERS-CoV in 2012. In late 2019, the Wuhan province of China started reporting numerous cases of pneumonia-like severe respiratory illness of unknown cause [2]. Within a short period of time, this emerging viral infection was referred to as "COVID-19" by the World Health Organization (WHO) and the novel beta-coronavirus

earned the title Severe Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [3] by the International Committee on Taxonomy of Viruses [4]. At present, the disease has become pandemic as declared by World Health Organization (WHO), affecting nearly 200 countries across the globe. In India alone, a staggering 77, 59,640 people have been infected, with 1, 17,236 deaths (latest on October 22, 2020). Globally, more than 41,869,297 people have been affected resulting in 1,140,555 deaths [5], in addition to huge secondary losses to the economy worldwide. Interestingly, the virus SARS-CoV-2 has a genomic sequence that is closely related to its predecessor Severe Acute Respiratory Syndrome (SARS) virus of 2003. This deadly virus most likely originated in bats and is assumed to have initially been transmitted from an animal reservoir to humans through an amplifying host [6]. It is however, the human-to-human transmission that has resulted in a sustained pandemic spread of this severe human infection. The nCoV-19 has surface glycoproteins by which they attach to human cells especially those that have specific Angiotensin-Converting Enzyme 2 Receptors (Ace2R) predominantly found in humans, dogs, bats, swine, non-human primates etc. [7]. Pangolins have been proposed to be the amplifying host as Pangolin-CoV has been shown to have 91.02% and 90.55% sequence similarity

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to SARS-CoV-2 and Bat-CoV RaTG13, respectively [8]. The S1 protein of Pangolin coronavirus is also much more closely related to SARS-CoV-2 than to RaTG13 [9].

Reports from various parts of China indicated that the most prominent COVID-19 cases reports severe-to-moderate pathophysiology [10]. The case fatality rate (CFR), which plays a pivotal role in the pathogenicity of the virus, especially during the course of infection, has been reported to be a higher percentage in the elderly male population with an average case fatality rate of 1–7%. Mexico has reported the highest case fatality rate of 9.95%; followed by Italy (7.93%), the United Kingdom (4.94%), France (3.42%), Russia (1.72%) and Spain (3.16%) [5]. A higher proportion of the elderly population, lower general immunity against pathogens, as well as life style problems have been suggested to be responsible for this huge mortality in these countries. Patients with comorbidities including hypertension, cardiac problems (heart injury) and diabetes mellitus have been reported to be at a significantly higher risk for COVID-19 infection. The general characteristics and infection mechanism of the virus is described in the next section.

## General Features & Basic Virology of SARS-CoV-2

Coronaviruses are widespread among humans and other vertebrates and are considered to be the major cause of various neurological and respiratory disorders. SARS-CoV-2 belongs to the Coronaviridae family [11] and are termed as Coronaviruses, because of the presence of their characteristic crownlike appearance made of surface glycoproteins. Mammals are reported to be infected by Alpha- and Beta-coronaviruses, whereas Gamma & Delta variants of the virus typically infect avian species. Coronaviruses consists of a 30 kb + single stranded positive RNA genome that encodes a number of open reading frames. One frame encodes the spike (S) protein which helps the virus to attach to cell surface receptors followed by its uptake into the endosomes where the S protein is further cleaved by furin like proteases found in many coronaviruses. The other major frame of the genome codes for structural and accessory proteins. The 5′ cap structure and 3′ poly (A) tail plays an important role in the expression of the replicase that constitutes nearly two third of its genome [12]. A number of non-structural proteins are also present which are generated by processing of different viral protease encoded within the replicase.

SARS-CoV-2 appears to be much more transmissible [13], despite the fact that it shares nearly 79% genome with the formerly known SARS-CoV. Chemosensory (smell and taste) and gustatory dysfunctions are found to have been strongly affected in COVID-19 patients and is emerging as one of the pivotal interpreters of COVID-19 infection [10].

The surface glycoproteins of the SARS-CoV-2 mainly bind to the cell via the angiotensin-converting enzyme 2 (ACE2) receptors on the alveolar epithelial cells [14], thus infecting the lower airways. The innate immune cells use the Pathogen Recognition Receptors (PRR) to recognise these viral antigens and activate immune signalling pathways [15] to produce various chemokines leading to activation of adaptive immune system. Progression of the infection has also been shown to lead to "Cytokine Storm" and is reviewed in detail later. Many accessory proteins that may contribute to the pathogenicity of the virus have not yet been characterized. ACE2 receptors are not only present in humans but also found in dogs, bats, swine as well as in non-human primates which both explains the animal origin as well as raises questions on the infectivity of this virus in a non-human host as well. The first human to cat transmission was reported from Belgium after a cat was found to be infected with SARS-CoV-2 from its owner as reported on March 27, 2020 [16]. Interestingly, the feline ACE2 protein is the homologue of human ACE2, which is the major cellular receptor used by the virus for entering into the cell [16]. The Bronx Zoo authorities have also confirmed that 4 tigers and 3 lions had been tested positive for this novel coronavirus on April 5, 2020 [17].

The current global focus is the development of diverse treatment regimes keeping in minds both short term treatment goals as well as long term sustainable immunity development prospects. This includes the development of novel therapeutics and antiviral drugs, use of cytokines and antibody as well long term sustainable vaccine development against the challenge. The following sections of the review look at each of them individually.

## Antivirals and Novel Therapeutics

Development and search of novel therapeutic agents to control this infection is an absolute need of the hour. The compounds that bind to the virus as well as specific inhibitors inhibiting fundamental processes such as replication & transcription as well as host cell protease and host cell endocytosis inhibitors need to be evaluated as possible therapeutics [18]. This includes both searches for novel drugs and their targets as well as repurposing of FDA approved drugs. The latter is slightly advantageous as clinical trials will be easier to conduct given that such drugs have already been proved safe for human usage. Clinical trials with a single addition of Ivermectin, an FDA approved anti-parasitic drug to Vero-hSLAM cells 2 h post infection have shown promising broad-spectrum antiviral activity against SARS-CoV-2 in vitro with nearly 5000 fold reduction in viral RNA at 48 h [19]. A common nucleoside analogue, Remdesivir works against coronaviruses that are closely related to

SARS-CoV-2 in animal models and also against MERS in non-human primates leading to termination of RNA synthesis and incorporation of mutagenesis [20]. Combination therapy of Remdesivir and Chloroquine has also been found to be effective against a clinical isolate of SARS-CoV-2 in vitro [21]. In another clinical trial Favipiravir, a drug that targets the RNA-dependent RNA Polymerase (RdRP) has been shown to be more effective than Arbidol with a reduction of fever, cough, and other adverse effects within 7 days [22]. Retroviral drugs have also been very promising against coronavirus infections. The combination of protease inhibitors Lopinavir and Ritonavir was used as a treatment for SARS-CoV and had shown promising results [23]. Ritonavir plays an important role in accelerating the half-life of Lopinavir by inhibiting the cytochrome P450 [24]. Scientists are also hopeful about the possible efficacy of Arbidol, a fusion inhibitor [25], as well as ASC09F (HIV protease inhibitor), Darunavir, and Cobicistat.

One of the most striking features of SARS-CoV-2 is that its RNA-dependent RNA polymerase (RdRp) sequence has a 96% identity to that of SARS-CoV, leading to widespread assumption that drugs developed for SARS-CoV RdRp may show similar efficacy for SARS-CoV-2 [26]. The anti-malarial drug Hydroxychloroquine, along with its anti-inflammatory function has been shown to inhibit SARS-CoV-2 infection in vitro. Though hydroxychloroquine is less toxic than Chloroquine, yet a high dose of it may lead to poisoning [27]. Researchers of Qingdao University of China have reported the efficacy of a phosphate derivative of Chloroquine against COVID-19 associated pneumonia in some clinical trials [28]. A clinical trial of Hydroxychloroquine in combination with Azithromycin has also been found to be effective in some cases [29].

As mentioned earlier, ACE2-R is the main target for the virus. This binding has also been shown to affect the balance of renin-angiotensin system leading to pneumonia and other chronic respiratory disorders. Therefore, Angiotensin-Converting Enzyme I (ACE-I) and Angiotensin type-1 receptor (AT1R) inhibitors might be able to reduce pulmonary inflammatory responses and is being currently explored as a possible intervention [30]. Implementation of combination therapy can also be an interesting option for the development of appropriate preventing and control strategies. Lopinavir and Ritonavir, in combination with Ribavirin have earlier shown promising therapeutic efficiency and clinical response among SARS infected patients and thus merits randomized placebo controlled trial among patients infected with SARS-CoV-2 [23]. At present, hospitals and health care centres of China are also using neuraminidase inhibitors [18].

In addition to antivirals, other possible therapy includes the use of siRNA, anti-sense RNA and ribozyme, peptide targeting S2, as well as natural products [31]. Scientists have cloned, tagged, and expressed a number of proteins in human cells and identified SARS-CoV-2-human protein–protein interactions that may act as effective molecular targets for antiviral drugs [32]. A bottleneck in this understanding and further commercialization is the lack of interest among the pharmaceutical companies owing to less availability of approved commercially available vaccines and therapeutic agents against CoV-2. PAC-MAN has emerged as an important CRISPR-Cas13 based strategy for the inhibition and degradation of viral RNA. It has been found that CRISPR RNAs targets 90% of all coronaviruses by cleaving their respective target sequences [33]. Scientists have already analysed therapeutic targets for SARS-CoV-2 and screened and identified potential drugs by computational approach [34]. In a study, important targets such as 3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp), and Papain-like protease (PLpro) were validated which will provide new insights to treat SARS-CoV infections [34].

Over the past decades, Natural products and their derivatives gained considerable importance as a major source of therapeutics. The source of some of the natural products and flavonoid compounds along with their respective targets [34] has been tabulated (Table 1) which may pave the way for future drug discovery. It must be stressed though, that the use of alternative and complementary medicines like Homoeopathy, Ayurveda against COVID-19 remains obscure and requires extensive investigation.

## Cytokine Storm in COVID-19-Therapeutic Intervention

The membrane fusion and cytoplasmic entry of SARS-CoV-2 is highly dependent on the priming reaction of S protein triggered by the serine protease TMPRSS2 [41]. Pulmonary type-II pneumocytes are included in the cellular entry which provokes an initial immune response with the production of inflammatory cytokines accompanied by a weak interferon (IFN-λ) response [42]. This response is followed by the chemotactic infiltration of monocyte-derived macrophages and neutrophils into the lung tissue, often resulting in a cytokine storm which is characterised by organ damage and massive immune cell infiltration [42]. A thorough understanding of the cytokine storm during the progression of COVID-19, as well as mechanisms to block infiltration and inflammation, will thus prove to be highly critical for patient treatment and controlling mortality rates [43]. Since Interleukin-6 (IL-6) has been shown to play a very important role; a possible therapeutic intervention might be obtained if the signal transduction pathway of IL-6 could be blocked [44]. Tocilizumab is an IL-6R blocker that is capable of blocking the IL-6 signal transduction pathway; hence this monoclonal

**Table 1** List of natural compounds and their targets against SARS-CoV-2

| Targets | Functions | Natural products | Source |
|---|---|---|---|
| Papain-like protease | Prevents RNA synthesis and replication [35] | Platycodin | *Platycon glandiflorus* |
| | | Baicalin | *Scutellaria baicalensis* |
| 3C-like main protease (3CLpro) | Plays an important role in maturation of Nsps (Non-structural proteins) which is a requisite for the life cycle of corona virus [36] | Betulonal | *Cassine xylocarpa* |
| | | Isodecortinol Cerevisterol | *Viola diffusa* |
| | | Chrysin-7-*O*-β-glucuronide | *Scutellaria baicalensis* |
| RNA-dependent RNA Polymerase (RdRp) | The conserved protein Nsp12 is an RdRp, which is the vital enzyme for replication-transcription machinery of corona virus [37] | Betulonal | *Cassine xylocarpa* |
| | | Gnidicin Gniditrin | *Gnidia lamprantha* |
| | | 3,3′-di-*O*-gallate | *Camellia sinensis* |
| Helicase | Nsp13 unwinds DNA and RNA along the 5′–3′ direction and requires NTP [38] | Phyllaemblicin-B Phyllaemblinol | *Phyllanthus emblica* |
| | | α-glucosyl Hesperidin Hesperidin Rutin | *Seratia* genus |
| Inhibition of viral structural proteins | Targeting Spike proteins and various receptors that are present on the host [39] | Licoflavonol | *Glycyrrhiza uralensis* |
| | | Cosmosiin | *Scutellaria baicalensis* |
| | | Neohesperidin | *Citrus aurantium* |
| Inhibition of virulence factors | Nsp1, Nsp3c and ORF7a are the three important virulence factors that affects host's innate immunity by causing mRNA degradation, Inhibition of type I interferon production and resisting host innate immunity, respectively [40] | Piperacillin Cefpiramide lymecycline | *Platycodon grandifloras* |
| | | Wogonoside | *Scutellaria baicalensis* |
| | | Vitexin | *Vitex negundo* |
| Inhibition or blocking of host specific receptors and enzymes | ACE2 is the specific receptor of Spike RBD of SARS-CoV-2 and blocking this receptor will inhibit entry of virus into host cells [14] | Phyllaemblicinn G7 | *Phyllanthus emblica* |
| | | Neohesperidin Hesperidin | *Citrus aurantium* |

antibody (MAb) is being tried as a possible drug for treating critical COVID-19 patients [45]. Similarly, Ruxolitinib (a JAK1/JAK2 inhibitor) has been shown to mitigate the cytokine storm in COVID-19 patients [46]. A human anti-Interleukin-6 receptor called TZLS-501 may help in preventing lung damage & chronic inflammation by reducing the amount of IL-6 during cytokine storm and organ infiltration in COVID-19 patients [47]. Dexamethasone has shown promise as an effective treatment in severe cases of COVID-19 that was caused owing to cytokine storm [48]. A neutralising antibody TJM2 produced by I-Mab-Biopharma may act as an effective treatment against the "Cytokine Storm" [49], as this antibody has been shown to work by targeting the Granulocyte Macrophage Colony Stimulating Factor that is responsible for chronic and acute inflammation [49]. Other specific modulators such as IL-1

receptor antagonists (Anakinra, Siltuximab), Janus kinase inhibitors (Baricitinib, Ruxolitinib), anti-Tumour Necrosis factor- α (TNF-α) (Adalimumab) etc., may also prove to be promising candidates [43].

## Interferon Therapy Against Coronavirus Infections

The interferons (IFNs) are a group of secreted cytokines that elicit distinct antiviral effects. In particular, IFN-α and β are induced in response to viral infections. These act through a common heterodimeric receptor to activate transcription of a diverse set of genes, referred to IFN-inducible genes or IFN-stimulated genes, whose protein products are mostly either directly/indirectly antiviral

in nature. These cytokines have also been reported to modulate the immune system by activating effector cell function, in addition to promoting the development of the acquired immune system [50].

Not surprisingly, Interferon therapy is being widely used for many viral diseases. Many of the IFN drugs are usually injectable, and companies now often produce them in combination with other molecules that leads to increase their life-span in blood. Cuban recombinant human Interferon alfa-2B has been proven effective against various viral infections [51]. The combination of lopinavir-ritonavir and Interferon-1β has been evaluated for MERS in the "MIRACLE" trial [52]. Interferon-β has been previously reported to reduce viral loads through improvement in pulmonary function, although it does not reduce viral replication and severe lung pathology against MERS-CoV infections [53]. In vitro inhibition in the growth of HIV has been observed through synergistic action of IFN-α and Azidothymidine [54]. IFN-α has also emerged as a convenient treatment for patients with papillomavirus warts of the larynx and skin (common warts) [54]. Pre-treatment with a single dose of mDEF201 intranasally has been shown to confer protection against SARS-CoV infections in mice [55]. Interestingly a combination of Interferon alfa-2B and Ribavirin has also played a pivotal role in the inhibition of Beta-coronavirus replication in vitro [56]. In line with other works, Lokugamage et al. have shown that SARS-CoV-2 is highly sensitive to interferon pre-treatment [57]. However, interferon administration can be lethal if their administration is not properly controlled. In a study by Channappanavar et al., it has been reported that delayed IFN-I signalling leads to tremendous accumulation of highly pathogenic inflammatory monocyte macrophages which can lead to elevation of cytokines and chemokines in the lungs accompanied by impaired virus specific T cell responses [58]. Interferon therapy thus might emerge as a promising choice in combating the SARS-CoV-2 infections; although identification of its target and its role in immunomodulation requires further investigation.

## Antibodies and Passive Immunization

Passive Immunization is defined as the transfer of antibodies to another individual who is at a risk of infection for the treatment of a disease. Direct or indirect administration of mAbs may help in combating against this pandemic. Previously, human monoclonal antibodies have been developed targeting the HR1 and HR2 domain of the spike protein as well as other viral proteins of SARS-CoV [59]. Leronlimab, a humanized monoclonal antibody specific to the chemokine receptor CCR5 that mitigates cytokine storm is currently under evaluation in a small number of patients experiencing respiratory complications owing to SARS-CoV-2 [60]. The therapeutic and clinical efficiency of Sarilumab, another IL-6 inhibiting monoclonal antibody is also under investigation [61]. Recently, a novel SARS-CoV specific monoclonal antibody CR3022 has been identified which binds to the receptor binding domain of SARS-CoV-2 and is emerging as a promising candidate for the treatment of COVD-19, as a whole or in combination with neutralizing antibodies [62]. In case of MERS infections, mAbs that bound with the epitopes of receptor binding, membrane fusion, and sialic acid binding sites of MERS S protein such as MERS-4, MERS-27, LCA-60, CDC2-C2 had emerged as a possible therapeutic intervention [63]. The mAbs that are specific to the receptor binding domain of SARS-CoV has a cross neutralizing capacity that will enable researchers to evaluate its efficacy against SARS-CoV-2. With the recent advancement in technology, human chain antibodies and humanized nanobodies against SARS-CoV-2 is a possibility; much like the ones used against pathogenic viral diseases such as Dengue, Ebola etc. An advantage of these nanobodies is that they can traverse across the biological membrane and interfere with the viral replication proteins resulting in inhibition of viral replication [64].

Serum therapy and use of plasma (Convalescent Plasma therapy) are also currently evolving to counteract attacks of SARS-CoV-2 and other pathogenic epidemics as clinical trials are currently being carried out in China against this emerging infection [65]. China has reported the efficacy of Convalescent Plasma therapy in improving the clinical circumstances of the severe COVID-19 patients through its clinical benefit, optimal dose, and its time of intervention requires further investigation in larger well-controlled trials [66]. The United States, Italy, India (in most of the states of the country, as approved by the Indian Council of Medical Research) have also started exploring convalescent plasma therapy against COVID-19.

## Comorbidity Treatment Regimes for COVID-19 Patients

Numerous evidences from the global pandemic have clearly pointed out that individuals with pre-existing comorbidities are significantly at a much higher risk of dying from COVID-19 [67]. Thus it is necessary to explore the biological mechanisms that lead to this risk for the development of appropriate therapies and repurposed treatments.

### Hypertension

Patients suffering from hypertension are currently at the highest risk of severe infection and mortality. ACE inhibitors (ACI) and Angiotensin receptor blockers (ARB) are used to

treat COVID-19 patients suffering from hypertension [68]. Studies have also revealed that those patients who were treated with non-ACI/ARB suffered from other additional comorbidities [69].

## Cardiovascular Disorders

Severe cardiovascular complications such as myocarditis, acute coronary syndrome, cardiogenic shock, heart failure as well as coagulation abnormalities are shown to develop in COVID-19 patients [70]. Coagulation abnormalities are characterised by elevated levels of prothrombin, fibrinogen, D-dimer, C-reactive protein (CRP), etc. [71]. Normally patients with cardiac problems are treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Besides calcium channel blockers are also used [72]. However, in case of heart attack, β-blocker, Diuretics, ARNI (Angiotensin receptor-neprilysin inhibitors) are generally used [73]. Antiplatelets, β-blockers, ACE inhibitors, and Nitrate group of drugs are used for COVID induced acute myocardial infarction [72]. Although there are some evidence of COVID-19 to be considered as a blood clotting disorder, yet the role of blood thinners in the prevention and treatment of blood clots in COVID-19 requires further investigations [74].

## Diabetes Mellitus

Type 2 diabetes is clinically featured by chronic inflammation and severe impairment in metabolism. Chronic inflammation in diabetic patients makes them much more susceptible to hyper-inflammation and cytokine storm [75]. Normally diabetic patients are treated with regular medications such as DPP4 inhibitors, Alpha glucoside inhibitors, SGLT2 inhibitors, Sulfonylureas, Metformins etc. In patients with moderate to severe COVID symptoms, insulin is being administered, while oral medications are being stopped. If the oxygen saturation falls below 95%; steroids like Dexamethasone are being used [76].

## Kidney Disorders

Patients with kidney disorders have been recommended not to stop their ACE inhibitors or ARBs to prevent sudden heart attack or other impairment in kidney function. Immunosuppressants are given to those undergoing kidney transplantation and suffering from COVID-19 [77]. Nephrologists recommend acetaminophen for pain relief and fever. Patients with chronic kidney disorders are usually advised to continue with their treatment of $Ca^{2+}$ metabolism drugs and Vitamin D, even on being infected with the virus. On the other hand, hemodialysis is a common treatment for acute

kidney disorders or kidney failure and is also advised to be continued [78].

## Liver Diseases

COVID-19 patients with significant liver damage or liver injury are being treated with regular hepatoprotective, anti-inflammatory, and jaundice reducing agents such as polyenephosphatidylcholine, glycyrrhizic acid, and vitamin E [79], depending upon the liver function injury and its associated symptoms. This is to be noted that Glycyrrhizin which was a preferred anti-inflammatory drug against acute liver damage has been found to have strong antiviral activity against SARS-CoV-2 [80].

## Respiratory Disorders

COPD (Chronic obstructive pulmonary disease) patients are very much susceptible to severe pneumonia upon infection with SARS-CoV-2 owing to enhanced expression of ACE2 receptor in the respiratory airways. The common respiratory medications given to COPD patients include inhaled and systemic corticosteroids, long-acting $β_2$-agonists, and muscarinic antagonists [81]. But whether these medications mitigates or exacerbates COVID-19 infections remains obscure till date. Previously it has been found that the use of corticosteroids has resulted in increased mortality and delayed viral clearance against MERS [82]. However, a controlled trial of Dexamethasone ("RECOVERY" trial) conducted in the United Kingdom showed a one-third reduction in mortality [83]. Bronchodilators are frequently administered via nebuliser in hospitalised patients with severe symptoms of COVID-19 [84]. Critical patients having hypoxemic COPD and COVID-19 are given controlled oxygen therapy as the first line treatment.

## Beta Coronavirus Vaccine Design: A Retroprospective Overview

Although there is extensive research on the previous SARS-CoV and MERS-CoV, yet there are neither licensed neither vaccines nor therapeutics to combat these infections. Thus it is of utmost importance to develop vaccines or post-exposure prophylaxis not only for the current pandemic but also for the prevention of future epidemics.

Information collected from past studies on SARS-CoV and the related MERS-CoV vaccine efforts have highlighted the fact that the spike glycoprotein is an ideal target for vaccine design. Recent studies on determining the structure of SARS-CoV-2 receptor binding domain (RBD) have shown that although ACE2 is the major cell receptor in both SARS-CoV-2 & SARS-CoV, the spike protein of the former binds

**Table 2** Current status (as updated on October 22, 2020) of the different SARS-CoV-2 vaccines in various stages of development

| Sl no | Type of vaccine | Name of the vaccine | Phase | Manufacturer (Company/university) | Features |
|---|---|---|---|---|---|
| 1 | Nucleic acid vaccine (Genetic vaccines) | mRNA-1273 | III | Moderna and Vaccine Research Centre in collaboration with National Institutes of Health | Vaccine targets the spike glycoprotein of Coronavirus and has been found effective in monkeys. Human trials yielded promising results [98] |
| | | mRNA based vaccine | III | BioNTech, Pfizer and FosunPharma | Shown to produce sufficient antibodies against SARS-CoV-2. Showed side effects like fever, fatigue [97] |
| | | DNA based vaccine | II | Zydus Cadila | Vaccine is delivered by skin patch. Phase 2 trial started in August 2020 [97] |
| | | mRNA based vaccine | II | CureVac | Phase 3 trials to start by end of 2020. Approval within 2021 tentatively [97] |
| | | Self amplifying RNA Vaccine | I & II | Imperial College of London and Morning-side Ventures | Production of viral protein through stimulation of immune system [97] |
| | | DNA based vaccine | I & II | Anges, Osaka University and Takara Bio | Phase 3 by end of 2020 [97] |
| | | mRNA vaccine | I & II | Arcturus and Duke-NUS Medical School | Self replicating |
| | | DNA based vaccine | I (Paused) | InoVio | Vaccine is delivered into skin through electric pulses. No adverse side effects. Limitations in delivery device [97] |
| | | Other nucleic acid vaccines | I | Genexine, WalVax Biotechnology, Chullongkorn University, Entos Pharmaceuticals | Started Phase I trials [97] |
| | | mRNA based vaccine | Preclinical | Sanofi Translate Bio | Phase I trial by December 2020 [97] |

**Table 2** (continued)

| Sl no | Type of vaccine | Name of the vaccine | Phase | Manufacturer (Company/university) | Features |
|---|---|---|---|---|---|
| 2 | Viral vector based vaccines | Ad5 | III | Can Sino Biologics and Academy of Military Medical Sciences | Phase I and II trials showed a strong immune response. Approved by the Chinese as a "specially mentioned drug" in June 2020 and has been approved for limited use [97] |
| | | Gam-Covid-Vac | III | Gamaleya Research Institute, Russia | Vaccine has been approved in August 2020 for early use. Promising results in Phase I and II trials [97] |
| | | Ad26 | III | Johnson & Johnson | Completed Phase I and II trials in July 2020. Started Phase III in September 2020 though it has been paused owing to adverse side effects [97] |
| | | ChAdOx1nCoV-19 | II & III | University of Oxford and AstraZeneca | Adenovirus vaccine vector. The clinical trial has been conducted through screening healthy volunteers in the Thomas Valley Region. Half of the volunteers received the vaccine and the remaining half has received the meningitis vaccine (Control group). Phase I and II showed that the vaccine raised antibodies against SARS-CoV-2 but during Phase III transverse myelitis developed in one of the volunteer. Trial has been paused till date [97] |
| | | GRAd-CoV-2 | I | ReiThera and Lazzaro Spallanzani National Institute for Infectious Diseases | Launched trial in July 2020 [97] |
| | | Other viral vector based vaccines | I | Vaxart; Merck and Institute Pasteur; Hongkong University; German Centre for Infection Research; ImmunityBio | Launched their Phase I trials [97] |
| | | | Preclinical phase | Novartis | Treatment is based on gene therapy. Trial will start by late 2020 [97] |

**Table 2** (continued)

| Sl no | Type of vaccine | Name of the vaccine | Manufacturer (Company/university) | Phase | Features |
|---|---|---|---|---|---|
| 3 | Protein based vaccines | Microscopic particles based protein vaccines | Novovax | III | Phase I and Phase II showed promising results by eliciting a strong immune response. If Phase III succeeds, millions of doses will be available within 2021 [97] |
| | | Adjuvant vaccine | Anhui Zhifei Longcom and Chinese Academy of Medical Sciences | II | Phase II trials started. Vaccine is designed based on the combination of viral proteins and adjuvants [97] |
| | | Soberana 1 | Finlay Vaccine Institute | I & II | Vaccine is made up of a portion of spike protein and adjuvant that can elicit a strong immune response [97] |
| | | EpiVacCorona | Vector Institute, Russia | I & II | Second vaccine (after Sputnik V) that has been approved by the Russian Government for early use before a phase III trial [97] |
| | | Adjuvant based vaccine | Sanofi & GSK | I & II | Phase I and II has been launched in September 2020. Vaccine will be available within 2021 if results are promising [97] |
| | | Other protein vaccines | Clover Biopharmaceuticals, University of Queensland, Medicago, Vaxine, Medigen, Adimmune, Covaxx | I | Started their Phase I trials recently [97] |
| | | | Baylor College of Medicine in collaboration with Texas Children Hospital PittCoVacc | Preclinical | The vaccine produces a significant amount of antibodies in mice. The Indian company Biological E licensed it. Clinical trials are expected to start by end October 2020 [97] Vaccine based on a skin patch tipped with needles. Trials are planned in late 2020 [97] |

**Table 2** (continued)

| Sl no | Type of vaccine | Name of the vaccine | Manufacturer (Company/university) | Phase | Features |
|---|---|---|---|---|---|
| 4 | Attenuated vaccines | Inactivated virus vaccine | Sinopharm and Wuhan Institute of Biological Products | III | Phase I and II showed a sufficient production of antibodies. Phase III is running presently and has been approved for limited use [97] |
| | | CoronaVac | SinoVac | III | No adverse effects found in Phase I and II. Phase III has been started in July 2020 and approved for limited use by the Chinese government [97] |
| | | Inactivated virus vaccine | Chinese Academy of Medical Sciences | II | Started Phase II in June 2020 [97] |
| | | COVAXIN | Bharat Biotech, Indian Council of Medical Research (ICMR) and National Institute of Virology, Pune | II | Vaccine has been found effective in hamsters and monkeys. Will be available in the middle of 2021 [97] |
| | | Qazcovid | Research Institute for Biological Safety Problems | I | Registered for Phase I trial in August 2020 [97] |
| 5 | Repurposed vaccines | BCG vaccine | Murdoch Children's Research Institute, Australia | III | Phase III trial termed as "BRACE" started in September 2020 [97] |

approximately 10 times more tightly than the latter [85]. The antisera induced by the receptor binding domain of SARS-CoV exhibits cross neutralization with the SARS-CoV-2 and thus may emerge as potential candidates for developing vaccines against both the infections. However, a problem in the vaccination strategy of SARS emerged the fact that although proven safe and immunogenic, the animals undergoing vaccination had shown significant disease as well as clinical symptoms upon challenge. For example, severe complications like lung damage and infiltration of the eosinophils in mice were reported, despite vaccination with live viral strains [86]. Although vaccination against SARS-CoV and MERS-CoV is associated with enhanced survival, reduction in virus titers, and/or less morbidity as compared to unvaccinated animals in animal models [87], an ideal vaccine developed for SARS-CoV-2 should preferably be less toxic, safer, and requiring less dosage. Scientists have identified a potent fusion inhibitor targeting the HR1 & HR2 domain of spike glycoprotein that could be used for treatment and prevention against SARS-CoV-2 and other SARS-CoVs [88]. Previously, antiviral lipopeptides having in-vitro fusion inhibition capacity have been genetically engineered as a prophylaxis treatment against the Nipah virus [89]. During the outbreak of SARS virus, Subunit vaccines have also been found to generate a strong and robust immune response against the spike protein that prevents it to dock with the host ACE2 receptor through induction of neutralizing antibodies [90]. Viral vectors like Rabies virus can also be a suitable option as it produces significantly higher levels of antibody response and cellular immunity [91]. Immunoinformatics and Molecular dynamics simulation studies revealed that the Cytotoxic T lymphocytes (CTL) epitopes and spike protein epitopic region interacts with MHC-I and MHC-II peptides and these epitopes can act as excellent targets for the design of effective vaccines against SARS-CoV-2 [92]. These targets might be helpful in designing a cost competitive, safe, less toxic vaccine with high therapeutic efficiency in humans against the virus.

## Recent Advancement in Vaccine Development Around the Globe

Vaccination has made one of the greatest contributions in human health through the successful eradication of the Small Pox and the near eradication of Polio. The current outbreak of COVID-19 highlights a significant ongoing need for the rapid design, production, and testing of candidate vaccines. This crisis has accelerated the development of novel coronavirus vaccines by multiple pharmaceutical companies and research organisations. For example, The Canadian Institute for Health Research (CIHR) is funding Medico for developing drug candidates and antibodies against SARS-CoV-2

in collaboration with the Disease Research Centre of Laval University [93]. Scientists have already shown that avian infectious bronchitis (IB) vaccine strain H, may be beneficial in people suffering from SARS infection [94]. Taking this idea into consideration, the Infectious Bronchitis Virus (IBV) has been modified genetically by the MIGAL Research Institute in Israel and will hopefully be available in oral forms soon. Kim and his colleagues have established a microneedle array based recombinant vaccination strategy which is capable of inducing virus specific potent antibody responses against SARS & other emerging infectious pathogens [95]. The Texas Children Hospital Centre for Vaccine development, in collaboration with the University of Texas and New York Blood Centre, has developed a subunit vaccine that has shown to have a higher protective immunity on viral challenge when formulated on alum [96]. The Italian Company Takis has developed an RNA vaccine against the gene that codes for the spike protein of SARS-CoV-2 and is expected to start its human trial shortly [97].

The status of the different vaccines currently under development and/or trial has been summarized in Table 2.

## Conclusions

Researchers around the world are racing for effective and suitable vaccine candidates and novel therapeutics for controlling the deadly COVID-19. Typically, the clinical development of a vaccine proceeds with small phase I trials for safety evaluation through formal toxicology testing in humans, followed by phase II trials through dosage formulation and phase III trials, in which the efficacy and safety of a vaccine are evaluated in a larger group. All of the therapeutics and vaccines also must be tested in an appropriate animal model before human trials. However, in this case, it has to be noted that the virus does not grow and infect wild-type mice, which has been shown to exhibit only mild clinical symptoms [86]. Despite all the odds, consolidated efforts on research are the only way forward as the world awaits successful trials of therapies and vaccines to fight this pandemic and prepare for the next ones.

**Author Contributions** AB: Manuscript preparation, Idea development, and Manuscript revision; MS: Consultancy; AH: Manuscript preparation and Manuscript revision; AD: Manuscript preparation: OM: Idea development, Manuscript preparation, and Manuscript revision.

## Compliance with Ethical Standards

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