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Review Article

## A Retrospective Assessment of the Initial Phase of Covid-19 and its Implemented Treatment Strategies

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### Abstract

Coronaviridae is a typical type of viral family comprised of an exceptionally huge RNA genome with a characteristic appearance and a noteworthy propensity to move from creatures to people. Since the start of the 21st century, three exceptionally contagious and pathogenic coronaviruses have traversed the species boundary and caused lethal pneumonia, exacting serious episodes, and causing human wellbeing crises to an unfathomable extent. The COVID-19 pandemic, presumably, is the most wrecking one, over the most recent 100 years after Spanish influenza. To the quick assessment of the various methodologies for a capability to evoke defensive resistance and well-being to shorten undesirable resistant potentiation, which assumes a significant function in this virus's pathogenesis. Considering the forthcoming public health crisis, researchers around the globe are consolidating their logical scientific possessions and offering initial information in an unprecedented way. In this review, we have tried to summarize some of the SARS-nCoV2 treatments that essentially focus on the potential drugs including Lopinavir/Ritonavir, Favipiravir, Remdesivir, Chloroquine phosphate, Hydroxychloroquine, Arbidol, and so on. Other potential vaccine developments with their difficulties associated and their current status are also being addressed.

**Keywords:** Coronaviridae, COVID-19 pandemic, Corona Virus, Potential antiviral drugs SARS-CoV-2, Vaccine against SARS-CoV-2.

## Introduction

Severe acute respiratory syndrome (SARS) was first expressed as a disorder of unidentified etiology in China, in 2002. As referred to by the World Health Organization (WHO), the pandemic has spread to 29 nations. The report says that in tally, around 8096 people were exposed to SARS infection and out of which 774 deaths were recorded <sup>1</sup>. Recently, the worldwide outbreak of novel COVID-19, which is reported to be caused by SARS-CoV-2. SARS-CoV-2 is a novel beta coronavirus with sequenced genes ranging from 29.8k to 29.9k RNA bases <sup>2-3</sup>. The SARS-CoV-2 genome codes entail structural proteins, replicate proteins, and accessory proteins. The ORF1ab & ORF1a polypeptides are proteolytically divided into 16 nonstructural proteins designated as nsp1-16 <sup>4</sup>. Like SARS, the most destructive and fatal effects of SARS-CoV-2 have already created a huge impact worldwide <sup>5</sup>. SARS-CoV-2 affects the lower respiratory system and causes viral pneumonia; however, it might likewise influence the heart, gastrointestinal system, kidney, central nervous system, and kidney following multiple organ failure <sup>6</sup>. The purpose of this review is to clarify the advancement made in the improvement of SARS species and to determine the gaps in the scientific understanding that needs to be completed. By talking about and overcoming these challenges and implementing improvements made, an effective and safe vaccine can be achieved.

## Molecular biology of the COVID-19

SARS-CoV-2 falls under the family Coronaviridae, classified as a subfamily of the ortho-coronaviridae, the seventh member of this family that infects people. Its members have named afterward their crown-like appearance under an electron microscope caused by excess glycoproteins that help identify and bind to the cell receptor <sup>7</sup>. A few conspicuous features of this novel coronavirus suggest that they are from bat-origin. The genome sequences & phylogenetic analysis show that this novel coronavirus is nearly like that of bat-originated coronavirus (SL-CoV ZC45) <sup>8</sup>. All these novel coronaviruses contain intact ORF8 & ORF3 gene regions. These are typical features of bat-origin coronaviruses <sup>9</sup>. Another piece of proof supporting COVID-19 has bat origins in the presence of high levels of ACE2 receptor homology from an assortment of creature species, hence affecting these species such as intermediate chemicals or animal species of COVID-19 diseases <sup>10</sup>. In terms of genetic sequence ownership and phylogenetic reports, SARS-CoV-2 is altogether unique concerning coronavirus and can consequently be viewed as another beta coronavirus that taints people <sup>11</sup>. However, amino acid sequences for the seven stored ORF1ab domains used for the classification of Coronaviruses strains were 94.4% like the 2019-nCoV and SARS-CoV strains, suggesting that the two viruses are the same type, SARS-CoV <sup>12</sup>. Its genomes are usually composed of a 50-methylguanosine cap initially, a 30-poly-A tail at the

end, and a total of 6–10 genes in between the structural proteins, including spike (S), envelope (E), and the membrane (M) that makes up the viral coat, as well as the nucleocapsid (N) protein that binds to the viral genome, is translated from subgenomic RNA<sup>13</sup>. A portion of these proteins gets glycosylated from Golgi substances to form glycoproteins. The S protein is made up of glycosylated and is required for bacterial binding and is potentially infectious and binds the virus to infected cells. The S protein is recommended by host cell protease and is detected by the cellular receptors ACE2 and TMPRSS2. is said to be locked by the clinically proven protease inhibitor<sup>14-15</sup>.

### Immunological features associated with COVID-19

Mainly, flu-like symptoms and typical pneumonia, are the characteristic of SARS-CoV infection, usually like a normal cold and influenza and do not become severe, including cough, sore throat, and breathing problems<sup>16</sup>. Most patients also developed lymphopenia and pneumonia with characteristic pulmonary ground-glass opacity changes on chest CT. It attacks other significant organs in the body, like the kidneys, which may cause organ failure<sup>17</sup>. Recent studies have found that the virus may affect renal tubular cells and testicular cells due to the high expression of ACE2. It also found that COVID-19 destroys gastrointestinal bacteria which lead to problems with the digestive system, for example, loss of appetite, vomiting, and diarrhea<sup>18</sup>. Besides, a study in China with more than a thousand hospitalized patients shows more elevated levels of proinflammatory cytokines including IL-2, IL-10, IL-7, G-CSF, IP-10, MIP-1A,

MCP-1, and TNF $\alpha$  were seen in the COVID-19 severe cases<sup>19</sup>. These findings are consistent with MERS and SARS in that the presence of lymphopenia and "cytokine storm" may assume a noteworthy function in the pathogenesis of COVID-19. This so-called "cytokine storm" can trigger viral sepsis and lung damage caused by other problems including pneumonitis, respiratory failure, acute respiratory syndrome (ARDS), shock, body failure death<sup>20</sup>. Major viral host interaction may include delayed Type I IFN response during initial infection, hyperinflammatory conditions triggered by viral replication, influx of activated neutrophils and inflammatory monocytes/macrophages, production of specific antibodies & induction of Th1/Th17. In an initial study, one patient from a group showed peak specific IgM on day 9 after disease onset and then switched to IgG by week 2. Interestingly, antibodies from 5 patients of confirmed COVID-19 show some cross-reactivity with SARS-CoV, but not other coronaviruses. Besides, all antibodies from patients were able to deplete SARS-CoV-2 in an *in vitro* plaque assay, suggesting that there may be an increase in humoral responses<sup>21</sup>.

### Potential drugs for the COVID-19 treatment

Various potential drugs indicate promising antiviral activity against SAR-CoV2. The list of clinical trials utilizing drug compounds to treat COVID-19 patients in Table I. Currently, numerous drugs and medications are being utilized in health facilities worldwide to test their viability, including lopinavir/ritonavir, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, and so on<sup>22</sup>.

**Table I:** Some potential antiviral drugs for COVID-19 patients undergoing clinical trials identified at <https://clinicaltrials.gov/><sup>55</sup>

Compound	Phase	Clinical Trial number	Sponsors
Lopinavir/Ritonavir	Phase 3	NCT04321174	Darrell Tan
Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination	Phase 2	NCT04276688	University of Hong Kong, Hospital Authority
Chloroquine Phosphate (CQ)	Phase 2	NCT04328493	Oxford University Clinical Research Unit, Vietnam
Chloroquine Phosphate (CQ)	Phase 2	NCT04333628	HaEmek Medical Center, Israel
Hydroxychloroquine (HCQ)	Phase 3	NCT04330144	Gangnam Severance Hospital
Azithromycin- Hydroxychloroquine Combination or Hydroxychloroquine	Phase 2	NCT04336332	Rutgers, The State University of New Jersey
Remdesivir (GS-5734)	Expanded	NCT04323761	Gilead Sciences
Remdesivir (GS-5734)	Phase 3	NCT04292899	Gilead Sciences
Favipiravir (T-705)	Phase 3	NCT04336904	Giuliano Rizzardini
Favipiravir (T-705)	Phase 2	NCT04346628	Stanford University
Baricitinib	Phase 2/3	NCT04320277	Hospital of Prato
Baricitinib	Phase 2/3	NCT04340232	University of Colorado, Denver
Galidesivir (BCX4430)	Phase 1	NCT03891420	BioCryst Pharmaceuticals
Darunavir and Cobicistat	Phase 3	NCT04252274	Shanghai Public Health Clinical Center
Hydroxychloroquine, Oseltamivir, or Azithromycin	Phase 3	NCT04338698	Shehnoor Azhar
CamostatMesylate	Phase 1	NCT04321096	University of Aarhus
Arbidol (Umifenovir)	Phase 4	NCT04350684	Shahid Beheshti University of Medical Sciences
Arbidol (Umifenovir)	Phase 4	NCT04260594	Jiemiing QU

### 1. Lopinavir/ritonavir (LPV/r)

Lopinavir/ritonavir (LPV/r), a protease inhibitor produced by AbbVie Corporation, is utilized for treating HIV-1 disease. The synthetic structure of Lopinavir is (2S) eN-[(2S,4S,5S)-5-[[2-(2,6-dimethylphenoxy) acetyl] amino]-4-hydroxy-1,6-diphenyl-hexan-2-yl]-3-methyl-2-(2-xo-1,3-diazinon-1-yl) butanamide. It is the dynamic segment of this medication combination, which blocks the division of Gag-Pol polyproteins, bringing about the creation of youthful virus particles unequipped for infecting the patients further. In any case, LPV has no impact on cells having incorporated viral DNA. What's more, it just forestalls ensuing contamination of other vulnerable cells<sup>22</sup>. Pharmacokinetic studies have indicated that lopinavir is essentially utilized by CYP3A4 and delivers low fundamental focuses at the point when utilized alone. Nonetheless, the metabolism of lopinavir could be repressed by ritonavir. Consequently, a mix of these two medications could draw out the fundamental introduction to lopinavir and keep the lopinavir fixation in the flow for a more extended time<sup>23</sup>. Diarrhea and other gastrointestinal problems, asthenia, headache, and skin rashes are the most common side effects in adults taking LPV/r medication<sup>22</sup>. Recently, a clinical trial (NCT04321174) is selecting members to additionally assess the adequacy of LPV/r for treating COVID-19 patients in Table I.

### 2. Chloroquine phosphate

Chloroquine phosphate is a water-dissolvable compound with the structure of 7-chloro-4-((40-diethylamino-1-methyl butyl) amino) quinoline diphosphate, which is broadly utilized for treating malaria disease and immune system infections, like lupus (both discoid lupus erythematosus and fundamental lupus erythematosus) and joint pain. It is the main principal line infection changing hostile to rheumatic medications utilized for treating rheumatoid arthritis (RA) and it acts by hindering antigen introduction limit of dendritic cells, cytokine creation in macrophages, just as calcium and toll-like receptor (TLR) motioning in B, T, and other immune cells. Chloroquine is chiefly ingested from the gastrointestinal lot, and it may hinder the virus infection by expanding the endosomal pH required for virus/cell combination, just as by meddling with the glycosylation of cell receptors of SARS-CoV<sup>24</sup>. While patients reported few side effects in clinics when given the standard dose of chloroquine, the most serious side effects include retinopathy, cardiomyopathy, and neuromyopathy when given for longer periods, and acute toxicity of chloroquine occurred when a high dose was given quickly through parenteral routes<sup>22</sup>. Recently, numerous clinical preliminaries with chloroquine against 2019-nCoV were started in numerous medical care hospitals in Table I.

### 3. Hydroxychloroquine (HCQ)

Hydroxychloroquine (HCQ) is an aminoquinoline compound adjusted by chloroquine, with an N-hydroxyethyl side chain rather than the N-diethyl gathering of chloroquine. An expansion in hydroxyl moiety makes it profoundly water solvent and less harmful than chloroquine, while yet holding the antiviral action. The immunomodulatory systems are like chloroquine by hoisting the pH through amassing in lysosomes. In this way, HCQ interferes in the cycle of antigen introduction and perhaps constricting the inflammatory reaction by essentially diminishing the creation of pro-inflammatory factors in COVID-19 patients. A blend of HCQ and azithromycin likewise indicated synergistic impact, giving a substitute treatment system for SARS-CoV-2 infection. Although HCQ is a less harmful particle, harm happens with its drawn-out use and over-measurement, especially irreversible retinopathy, perhaps prompting the

loss of vision<sup>25</sup>. Hence, clinical checking and early acknowledgment of poisonous manifestations are fundamental for a viable administration procedure. Clinicians should screen the portion taken by the patients and pay close consideration regarding the side effects including neuromyopathy, retinal toxicity, and heart infection during clinical trials. Be that as it may, at present, there is still no reasonable proof to help the adequacy of HCQ against SARS-CoV-2 infection,<sup>26</sup> which stays to be affirmed by clinical trials in Table I.

### 4. Arbidol (ARB)

Arbidol (ARB), otherwise called umifenovir, is suggested as an explicit anti-influenza drug to control influenza A and influenza B. The drug has been endorsed in Russia and China for clinical use, with no major adverse effects reported to date. It forestalls contact between the virus and host cells and infiltration of virus particles into the cell by restraining the combination of the infection lipid shell to the cell membrane<sup>27</sup>. Hence, a review study affirmed by the Third People's Hospital of Changzhou, China exhibited the adequacy of ARB monotherapy, which may be better than LPV/r against COVID-19. In any case, the current information with clinical trials is deficient to unequivocally demonstrate the viability of ARB against COVID-19 as a result of the restricted example size, and the obscure antiviral mechanisms. Another examination affirmed that ARB combined with LPV/r may profit the patients by postponing the movement of lung sores and bringing down the chance of respiratory and gastrointestinal transmissions. Consequently, blend treatment could be the best method for the management of COVID-19, which should be approved sooner rather than later<sup>28</sup>. Several adverse effects were reported, the most common of which were gastrointestinal side effects and elevated transaminase levels<sup>22</sup>. At present, stage IV clinical trials are being completed to test the adequacy of ARB against COVID-19 counting NCT04350684 and NCT04260594 in Table I.

### 5. Remdesivir

Remdesivir (GS-5734), a prodrug created by Gilead Science, is all around perceived as an expected antiviral medication against a wide exhibit of diseases with RNA viruses in cell cultures, mice, and non-human primate (NHP) models. The anticipated mechanism of activity is by the joining of a functioning triphosphate into the viral RNA bringing about the untimely end of RNA synthesis that diminished the degree of viral RNA<sup>29</sup>. In 12% of the participants, serious side effects including hypotension, acute kidney injury, septic shock, and multiple organ dysfunction syndromes were recorded<sup>22</sup>. In any case, a report distributed in the New England Journal of Medicine depicted the impact of GS-5734 was yet lacking to evaluate in the first COVID-19 patient recovered after Remdesivir infusion in the United States because the viral heap of the patient was diminished before Remdesivir was utilized. Subsequently, the patient recovery was inferable from the medication or the job of self-defense mechanisms, and steady medicines were most certainly not clarified<sup>30</sup>. As of now, clinical trials utilizing GS-5734 as a remedial against 2019-nCoV infection are in progress (NCT04323761 and NCT04292899), and the adequacy and unfriendly responses of this medication are deserving of our consideration in Table I.

### 6. Favipiravir (FPV)

Favipiravir (T-705), 6-Fluoro-3-hydroxypyrazine-2-carboxamide, is a novel RNA-dependent RNA polymerase (RdRp) Inhibitor from Toyama Chemical Co., Ltd, and is used to treat common flu infections in Japan. Favipiravir-RTP



(favipiravir ribofuranosyl-50-triphosphate) is the dynamic type of T-705 changed over by chemicals, which goes about as a nucleotide analog selectively hindering the RdRp. Simultaneously, T-705 can likewise get joined into the incipient viral RNA resulting at the end of the viral replication measures. Another examination looked at the impacts of FPV and LPV/r for treating Coronavirus patients. FPV would do well to treatment consequences for COVID-19 contrasted with LPV/r having a quicker viral clearance rate and a higher level of progress from lung entanglements as proven by imaging methods<sup>31</sup>. In any case, the creation and use of T-705 are seriously limited in Japan as a result of the common dangers of teratogenicity and embryotoxicity<sup>32</sup>. Currently, a stage III clinical preliminary of T-705 (NCT04336904) is now in progress as in Table I.

## 7. Others' antiviral drugs

Ribavirin is known as a viable antiviral drug to battle the hepatitis C virus (HCV) yet it is profoundly cytotoxic<sup>33</sup>. Indeed, at that point, it was remembered for the suggested combination treatment with interferon or LPV/r in the diagnosis and treatment guidelines of the 2019-nCoV in China (the seventh version). Be that as it may, there was lack of proof accessible for its clinical adequacy after administration to COVID-19 patients. A Janus kinase inhibitor, baricitinib, which ties to the cyclin G-related kinase, is a controller of endocytosis. Analysts utilized AI to look for the affirmed medicaments that could help in the treatment of COVID-19 disease and found baricitinib as a potential drug to treat 2019-nCoV acute respiratory illness<sup>34</sup>. As of late, the clinical trials of baricitinib against COVID-19 (NCT04320277 and NCT04340232) are progressing and the outcomes are energetically anticipated<sup>35</sup>. Lanjuan Li group has indicated Darunavir, an HIV-1 protease inhibitor, has action against 2019-nCoV. Darunavir might be directed alongside either cobicistat or ritonavir. However, the adequacy and safety profile are yet to be investigated<sup>36</sup>. As of now, the stage III clinical trials of Darunavir along with Cobicistat against Coronavirus are in progress. Oseltamivir is a medication utilized for forestalling and treating influenza virus infection in children. It was gone after for the treatment of SARS-CoV-2 patients;<sup>37</sup> However, its adequacy stays dubious.

## Considerations in vaccine development

Demographic changes might affect the epidemiology of COVID-19 and so the retardation of the vaccine development process<sup>38</sup>. Previous clinical trials on vaccine candidates of the severe acute respiratory syndrome (SARS) have shown a deadly immune system interaction and those then exposed to the virus developed more complicated disease than those who were unvaccinated. This immune backfiring additionally called an insusceptible upgrade, may build up antibody-dependent enhancement (ADE), a cycle where a virus exploits antibodies to advance disease or a class of Th2 immunopathology that initiates hypersensitive inflammation in the patient<sup>39, 45-46</sup>. Cats immunized against fractional inactivated poliovirus vaccine (fiPV) got more diseased than cats who were not vaccinated<sup>40</sup>. It is to be found that reinfections by COVID-19 are possible because no hard immunity develops in the body even after getting cured of the infection<sup>41</sup>. Protective immunity develops after the second vaccination, which can be given after 3-4 weeks of the first shot and may last up to only one to two weeks. So, the vaccine to be developed should target to achieve a long-time immunity against the virus<sup>42</sup>. Due to the mutation and demographic variation of the virus, a detailed understanding of the genome & pathogenic mechanism of SARS-CoV is still not possible<sup>48-49</sup>. Different pathogenesis in animal models of

SARS-CoV infection couldn't reenact human disease<sup>51</sup>. Researchers found that normally lab-animals don't have the receptor-binding domains like humans. However, Bao *et al.* tested the pathogenicity of SARS-CoV-2 in ACE2 receptor-expressing transgenic mice show mild disease. So, here again, the vaccine development process will face a barrier to clinical trials<sup>43</sup>. Previous research claims that immune senescence occurs in older people aged 65 or above, which lowers the vaccine responses on them<sup>44</sup>. Clinical trial NCT04348370 is running to test the efficacy of the bacille Calmette-Guerin (BCG) vaccine on the COVID-19 pandemic but the WHO clearly stated that it does not recommend such vaccination against COVID-19<sup>54</sup>.

## Animal models

A remarkable advance in SARS research came with the discovery that ACE2 receptor overexpressed transgenic mice were prone to infection with SARS-CoV 2, Interstitial pneumonia & Specific IgG antibodies against S protein SARS-CoV-2 was positively measured in those mice<sup>46</sup>. From previous research, it is documented that domestic ferrets & cats can be a promising animal model for SARS-CoV. Ferrets show alveolar damage, elevated liver enzymes, and lymphocytic infiltration, which is quite like humans. A recent study also claimed ferrets & cats are highly permissive towards SARS-CoV2 infection<sup>39</sup>. These models are a promising contender for preclinical research yet don't completely mimic the clinical disease. SARS-CoV-2 causes disease in cynomolgus macaques like COVID19 which can be a novel infection model that can help in evaluating the efficacy of repurposing species-specific existing treatment. Patent application WO2017095875 mentioned the arrangement of human antibodies and immune conjugates explicitly focusing on chemokine IP-10, including an anti-IP-10 antibody, which appeared to stifle free serum IP-10 in around 3 days in Cynomolgus macaques<sup>40</sup>. The golden hamster or Syrian hamster also supports the SARS-CoV-2 infection and shows an immune response the same as humans when infected. It is also capable of transmission, so it could be a prompt model for vaccine development. However, a successful animal model trial cannot be considered as a clinically effective vaccine because of some higher physiological barriers in humans<sup>47</sup>. So, the usage of such models should be reduced to an extent. But the alternative models which may run on computers are not properly developed yet or need some more research. So, now our uttermost responsibility is to save human lives, which may cost some sacrifice<sup>48</sup>.

## Various vaccines mechanism of action

The best-authorized vaccines evoke long-haul antigen-explicit antibody responses by plasma cells notwithstanding the turn of events of persisting T cell and B cell memory. If there should be an occurrence of SARS-CoV infection, both humoral and cellular immune responses are critical for the freedom of infection<sup>38</sup>. Recombinant virus vectors work in a comparable way like an endogenous microbe, by communicating axenic target protein in the cytoplasm of the host cell. In the wake of handling of such endogenous antigen, MHC class 1 molecule presents them to CD8+ T lymphocytes, which causes the creation of T-cytotoxic cells. This pathway prompts the foundation of cell-interceded insusceptibility, which is urgent in disposing of virus-contaminated cells. Subunit vaccine applicants, especially RBD of S protein of SARS-CoV contain major antigenic determinants that can actuate killing antibodies. The SARS-CoV S protein can likewise actuate CD8+ T-cell reactions<sup>39</sup>. The RBD of S protein contains various adaptation subordinate epitopes and is the primary area that actuates

killing antibody and T-cell resistant reactions against SARS-CoV contamination, making it a significant focus for antibody improvement. The methodologies for creating RBD-based antibodies against SARS-CoV have given valuable data to planning safe and powerful immunizations against SARS-CoV 2 since RBDs of SARS-CoV 2 additionally contain comparative epitopes. Also, Adenoviral vectors can initiate intense antibody just as T cell reactions with varieties in the resistant reaction relying upon the serotype utilized. Replication-lacking Ad5, one of the most generally utilized adenoviral vectors, can initiate astoundingly intense CD8+ T cells just as antibody reactions <sup>49</sup>. Besides, DNA immunization is additionally ready to inspire both humoral and cell safe reactions, through actuation of CD8+ cytotoxic and CD4+ aide T cells, individually, upon a passage in the cell, DNA vaccines are detected by an assortment of innate insusceptible receptors, for example, STING/TBK1/IRF3 pathways and the AIM2 inflammasome and numerous different variables are associated with DNA immunization method of activity however the specific mechanism of action is yet to be assessed <sup>50</sup>. Nonetheless, inoculation with S protein-encoding DNA vaccine defensive invulnerability against SARS-CoV infection in a mouse model by instigating T cell and killing antibody reactions <sup>51</sup>.

## RNA viruses and challenges for vaccine development

RNA viruses recreate through RNA-subordinate, RNA polymerase encoded by the infection. This sort of polymerase has no editing instrument related to it, which brings about a high pace of uncorrected mutations <sup>1</sup>. These changes might be deadly to virus replication and may even continue, bringing about the fast development of the virus. Thus, numerous RNA infections have different genomic strains, or quasi-species, present at once in a person. Silent mutation in the RdRp gene has been noticed in North America & Italy, also in India where the maximum number of mutations were identified in Indian sequence-located in ORF1ab, nsp2, nsp3, helicase, ORF8 protein, and spike surface glycoprotein, and a unique mutation identified in the spike surface glycoprotein in the Indian sequence <sup>48</sup>. Most coronaviruses are thought to be able to replicate due to the homologous sequence at the end of 5 and 3 mRNAs. Evidence suggests that SARS-CoV was initiated by reunification between coronaviruses and that there was an increase in genetic diversity <sup>52</sup>.

## Potential vaccine candidates and prototypes

As per the DRAFT scene of COVID-19 candidate vaccines by WHO, major types include non-replicating viral vectors, DNA-based vaccines, mRNA-based vaccines, and inactivated virus and recombinant protein-based vaccine <sup>53</sup>. Table II shows a list of accepted patents regarding SARS vaccine development.

### Attenuated Virus Vaccines

This is an existing licensed human vaccine platform. It is a straightforward cycle utilized for a few authorized human vaccines; the existing framework can be utilized for large-scale manufacturing. Patent application US20060039926 reveals live attenuated coronavirus or torovirus immunizations. By the fifth day after intracerebral injection, the mice exhibited a low replication of the attenuated MHV virus. When all is said in done, the creation of irresistible clones for COVID vaccine seeds requires significant investment because of the huge genetic size (30.0 KB). Safety checks should be extensive <sup>4</sup>. For example, Indian Immunologicals Ltd/Griffith University, Codagenix/Serum

Institute of India, Mehmet Ali Aydinlar University/AciBadem Labmed Health Services are separately working on Live Attenuated vaccine targeting SARS-COV2, but all three are in the clinical trial phase <sup>39</sup>.

### DNA-Based Vaccines

This is a non-licensed vaccine platform. It mainly targets the Spike protein (S). Currently, DNA-Based vaccine candidates running in clinical trial Phase-1 for COVID-19 involves Patent application NCT04336410 which shows DNA plasmid encoding S protein. It is delivered by electroporation method named INO-4800 innovated by Inovio Pharmaceuticals planned for a human trial. Patent application WO2005081716 uncovers structures and techniques for instigating and improving resistant reactions, especially antigen-explicit CD8+ T cell-mediated reactions, against antigens of the SARS COVID-19. For example, as 12th April 2021 report by WHO on "DRAFT scene of COVID-19 candidate vaccines.pdf", only 4 out of 16 DNA Vaccine candidates got consent to direct a Phase 2 trial <sup>36,39</sup>.

### Recombinant proteins and virus-like particles

This is a partially licensed vaccine platform limited to baculovirus (influenza, HPV). It mainly targets the Spike protein (S). No irresistible virus should be taken care of, adjuvants can be utilized to expand immunogenicity. Patent application WO2010063685 by GlaxoSmithKline (GSK) reveals an immunization that can exasperate a defensive invulnerable reaction against SARS. The vaccine contains an oil-in-water emulsion adjuvant and S protein immunogen <sup>4</sup>. Patent US2007000357 describes Purified trimeric S protein as a vaccine against severe acute respiratory syndrome virus infections. For example, Genex announced a developing COVID-19 vaccine in patent US20060002947 describes li-key/antigenic epitope hybrid peptide vaccines. The organization will use its li-Key insusceptible framework initiation innovation to deliver a COVID-19 viral peptide for human clinical trials <sup>53</sup>.

### Viral vector-based vaccines

This is a partially licensed vaccine platform limited to VSV (Ervebo) but not for the viral vectored vaccines. It also targets Spike (S) proteins. No such irresistible virus should be taken care of, it as of now has some phenomenal preclinical and clinical information for some rising viruses, including MERS-CoV. Later, Vector insusceptibility may contrarily influence antibody viability (contingent upon the vector picked) <sup>4</sup>. For example, Viral-vector-based vaccines (focused on the S protein, e.g., Vaxart, Geovax, University of Oxford, and Cansino Biologics) J & J is using an experimental adenovirus vector platform that has not yet resulted in a licensed vaccine. As the 12th April 2021 report by WHO on "DRAFT scene of COVID-19 candidate vaccines.pdf", only 4 out of 43 viral vector Vaccine candidates can conduct phase 3 trial. Those four candidates are based on a non-replicating viral vector <sup>43</sup>.

### mRNA-Based Vaccines

Here, no such irresistible virus needs to be treated, vaccines are usually immunogenic, rapid production is possible. Safety issues with reactogenicity have been reported. The mRNA-based vaccine, which produces a target in vivo vaccine after injecting mRNA into lipid nanoparticles, has been produced in collaboration with Moderna and the vaccine research center at the National Institutes of Health. A clinical trial has just begun (ClinicalTrials.gov: NCT04283461). Curevac works with a nearly similar vaccine but it is in the clinical trial phase. Patent WO2017070626 application by Moderna produces mRNA drugs made from

mRNAs encoding antigenic viral full-length S, S1, or S2 protein from SARS-CoV and MERS-CoV infection, figured in cationic lipid nanoparticles. They reveal that mice inoculated with mRNA encoding Coronavirus full-length S protein delivered higher antibody titers contrasted with mRNA encoding the S protein S2 subunit <sup>50</sup>. As in 12th April 2021

report by WHO on "DRAFT scene of COVID-19 candidate vaccines.pdf", only 2 of the 23 mRNAs vaccines used to receive (one from Moderna and the other from BioNTech Pharmaceuticals) approval for a phase 3 trial and both are lipid nanoparticle-based delivery <sup>55</sup>.

**Table II:** List of some SARS-CoV-2 vaccine undergoing clinical trials currently and candidates for the development of a safe and effective Vaccine <sup>55</sup>.

Vaccine	Phase	Clinical Trial number	Institute	Sponsor
mRNA-1273	Phase-1	NCT04283461	Emory Vaccine Center-The Hope Clinic, Decatur, Georgia, United State	National Institute of Allergy and Infectious Disease (NIAID)
Gam-COVID-Vac	Phase-1/2	NCT04436471	Main military clinical hospital named after academician N. N. Burdenko Moscow, Russian Federation	Gamaleya Research Institute of Epidemiology and Microbiology, Russia
Pathogen-specific APC	Phase-1	NCT04299724	Shenzhen Genoimmune Medical Institute Shenzhen, Guangdong, China	Shenzhen Geno-Immune Medical Institute
Antigen-specific CTLs, injection and infusion of LVSMENP- DC vaccine	Phase-1/2	NCT04276896	Shenzhen Second People's Hospital Shenzhen, Guangdong, China	Shenzhen Geno-Immune Medical Institute
BNT162a1	Phase-3	NCT04368728	NYU Langone Health New York, New York, United States	Pfizer/Biotech SE
Recombinant novel coronavirus vaccine	Phase-2	NCT04341389	Hubei Provincial Center for Disease Control and Prevention Wuhan, Hubei, China	CanSino Biologics Inc.
BCG	Phase-4	NCT04369794	Hospital das Clínicas Unicamp Campinas,	University of Campinas, Brazil
SCB-2019	Phase-1	NCT04405908	Linear Clinical Research Ltd Nedlands, Western Australia, Australia	Clover Biopharmaceuticals, AUS Pty Ltd.
bac-TRL-Spike	Phase-1	NCT04334980	Canadian center for Vaccinology Dalhousie University, IWK Health Centre Halifax, Nova Scotia, Canada	Symvivo Corporation
Inactivated SARS-CoV-2 vaccine	Phase-1/2	NCT04412538	West China Second University Hospital, Sichuan University, China	Chines Academy of Medical Sciences
ChAdOx1 nCoV-19	Phase-3	NCT04324606	University Hospital Southampton NHS Foundation Trust Southampton, Hampshire, United Kingdom	University of Oxford
IMM-101	Phase-3	NCT04442048	Canadian Cancer Trials Group	Canadian Cancer Trials Group, BioCan Rx
INO-4800	Phase-1	NCT04336410	University of Pennsylvania Philadelphia, Pennsylvania, United States	Inovio Pharmaceuticals
Alum-adjuvanted, formalin-inactivated vaccine	Phase 1/2	NCT04282574	Renqiu City Center for Disease Control and Prevention, Renqiu, Hebei, China	Sinovac Research and Development Co., Ltd.
Alum-adjuvanted, formalin-inactivated vaccine	Phase 1/2	NCT04352608	Suining County Center for Disease Control and Prevention Xuzhou, Jiangsu, China	Sinovac Research and Development Co., Ltd.
Vectored vaccine: Adenovirus Type 5 Vector	Phase 2	NCT04313127	Institute of Biotechnology, Academy of Military Medical Sciences. PLA of China, Jiangsu Province Centers for Disease Control and Prevention,	CanSino Biologics Inc.,

			Hubei Provincial Center for Disease Control and Prevention, Tongji Hospital	
Vectored vaccine: Adenovirus Type 26 with spike protein	Phase 1/2	NCT04437875	Sechenov First Moscow State Medical University, Moscow, Russian Federation,	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation, Acellena Contract Drug Research and Development
Artificial APCs expressing SARS-CoV-2 proteins	Phase 1/2	NCT04386252	Hoag Memorial Hospital Presbyterian, Newport Beach, California, United States	Aivita Biomedical, Inc.
Nanoparticle vaccine with Matrix-M adjuvant	Phase 1	NCT04368988	Advanced Clinical Research, Meridian, Idaho, United States	Novavax

## Conclusion

Despite the serious study of SARS-COV2, more pieces of information are required to be revealed about the pathology of the virus. Many research-related quarries remain to be answered and effective drug or/and safe vaccines against SARS-COV2 infection, which is the need the hours remaining to be recognized. With a sensible plan of clinical openings, significant and logical research is essential to determine the effectiveness of the applied medications. We have tried to summarize some of the SAR-nCoV2 treatments that essentially focus on the potential drugs. Also, we need to know the components of viral virality and use this information to carefully develop the vaccines. To

comprehend viral pathogenesis, one must realize how the immune system intervenes with the virus. It is also justified to seek the production of several vaccine varieties, including those against other target antigens, to increase the chances of efficacy. The best choice for increasing the percentage of the population immune to SARS-CoV2 is to use vaccines that induce neutralizing antibodies on a wide scale. Herd immunity may be achieved by vaccination, while widespread natural infection tends to be too dangerous for humans and the economy, unless viral transmission induces immunity in far greater fractions of the world's population than currently understood and anticipated, probably in countries with laxer anti-viral steps. COVID-19 vaccination is given top priority due to the urgency.

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