# Proposed therapies and vaccine developing for COVID-19 (SARS CoV-2)

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## Abstract

COVID-19 or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the third spillover of animal coronavirus to humans, resulting in a major respiratory epidemic in less than two decades. In March, 2020 the World Health Organization (WHO) called this respiratory infectious disease as a "Pandemic Outbreaks", unfortunately, no drug or vaccine has yet been approved to treat COVID-19 (SARS-CoV-2). About 3.5 million confirmed cases and more than 240 thousand deaths worldwide were reported from this respiratory pandemic by May 03, 2020. This outbreak pushed the researchers and physicians to use "Drug repositioning strategy", in a trail to stop this pandemic infection until developing the suitable vaccination, which in best circumstances will not be available before January, 2021. A lot of drugs that have been previously developed as antiviral medications such as; Favipiravir, Ribavirin, Lopinavir/Ritonavir and Remdesivir, or other drugs used as antimalarial agents including; Chloroquine and Hydroxyl Chloroquine, are being tested for treating COVID-19. Along with the physician that aim to face this outbreak by using drugs already in market and try to repurpose it, the developer in drug design field also race against time, to find a new drug for COVID-19 beginning from drug design in silico, ending with clinical trials. More than 79 worldwide research companies/institutions in cooperation with many governmental sides, are working together to find a suitable vaccine for this virus, using many platform for vaccine discovery such as; mRNA, DNA, inactivated virus, attenuated virus, subunits and recombinant proteins. However, scientists believe that under the best condition, the vaccine will not be available before January, 2021. The aims of this review were to express the main trials for COVID-19 treatment via drug repositioning, as well as the movement of the companies and the different organizations towards finding a suitable active vaccine, before the crisis become improbable.

**Keywords**: Coronavirus; SARS CoV-2; COVID-19, Drug repositioning strategy, Vaccination

## 1. Introduction

In late December 2019, an outbreak of an emerging disease (COVID-19) caused by a novel coronavirus started in Wuhan, China, and rapidly spread in China and outside (Lai *et al*., 2020). Later, an epidemic of COVID-19 infection was declared by the WHO as a pandemic, on March 12th 2020 (Gautret *et al*., 2020). By the 11th of February 2020, the WHO announced the official name for the disease caused by this new coronavirus as COVID-19. Later, Gorbalenya *et al*., (2020) added that this name is converted to SARS-CoV-2 by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses. This committee is responsible for developing the official classification of viruses, and taxonomy of the *Coronaviridae* family. This viral name was chosen based on the analysis of the new coronavirus's evolutionary history, and the pathogen that causes severe acute respiratory syndrome (SARS). Thus, this new virus has been given the name as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

## 2. Structure of the COVID-19 virus

A recent study of Chen *et al*., (2020) described SARS-CoV-2 (COVID-19) virion as being of approximately 50-200 nm in diameter, +ve sense, and single-stranded RNA beta-coronavirus. Wu *et al*., (2020) reported that like the other coronaviruses, SARS-CoV-2 has four structural proteins mainly; the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The N protein holds the RNA genome, whereas the S, E, and M proteins together create the viral envelope (Fig. 1). Moreover, Guangdi and De Clercq, (2020) added that this virus has high percentage of similarity with the Severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS).

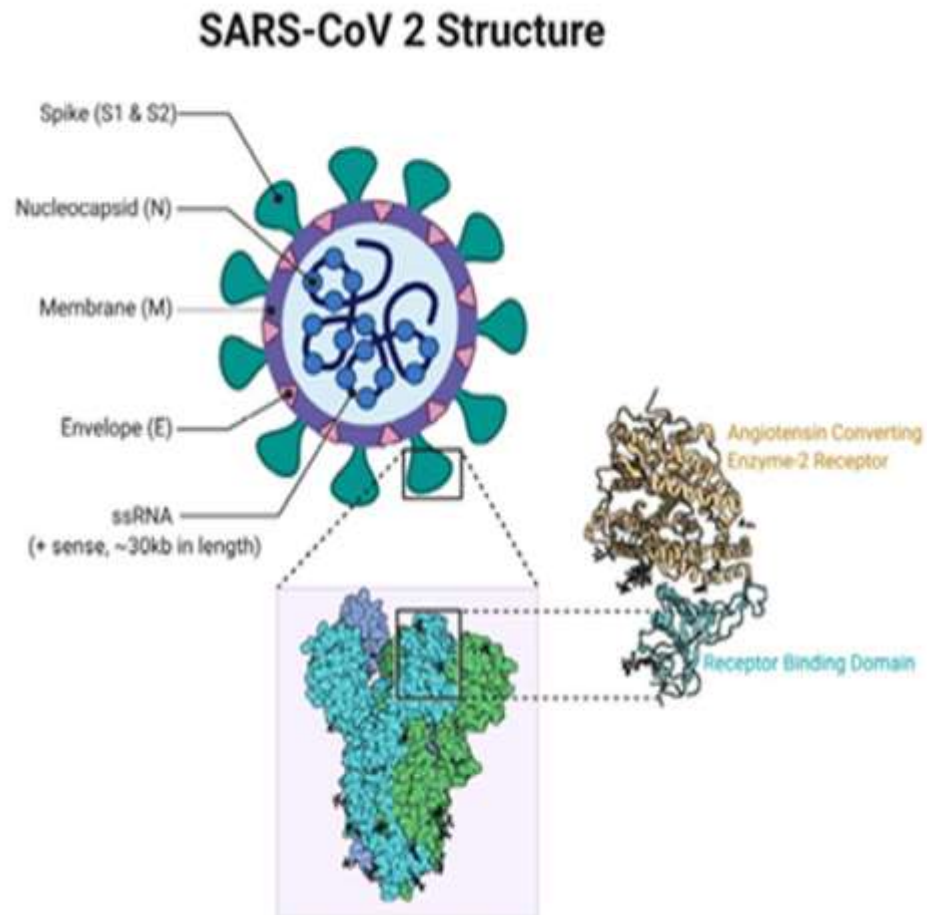Recent studies conducted by Wu *et al*., (2020); Xu *et al*., (2020) highlighted that the spike protein; which has been imaged at the atomic level using cryogenic electron microscopy, is the protein responsible for allowing the virus to attach to and fuse with the membrane of the host cell. Moreover, Zhang *et al*., (2020) added that the protein modeling experiments on the spike protein of the virus soon revealed that SARS-CoV-2 has sufficient affinity to the receptor Angiotensin Converting Enzyme 2 (ACE2) found on the surface of the human alveolar cells II, which was suggested as a mechanism of viral entry into the cell.

## 3. Symptoms of the viral infection

Symptoms of COVID-19 can be relatively non-specific and infected people may be asymptomatic. Fever is the most common symptom with a percentage of (88%), followed by dry cough (68%). Fatigue, sore throat, respiratory sputum production (phlegm), shortness of breath, loss of the sense of smell, muscle and joint pain, headache, chills, hemoptysis, diarrhea, vomiting or cyanosis are less common symptoms (Di Wu *et al*., 2020; Sin-Yee *et al*., 2020).

## 4. Methods of diagnosis of the SARS-CoV-2 (COVID-19) disease

Many diagnostic tools have been developed for detecting the presence of the COVID-19 virus, as the distinction of this viral disease from general cold infections is essential for proper treatment. Among these used tools is the: a)-Reverse transcription Real-time Polymerase Chain Reaction (rt RT-PCR). Ai *et al*., (2020) reported that the respiratory samples obtained using nasopharyngeal and oropharyngeal sputum or swabs can be used in this test for detecting the presence of the viral RNA. Test takes between 3 hours to 2 days with average 7 hours till end results have released. b)-Enzyme Linked Immuno Sorbent Assay (ELISA), which is a serological assay that can also be used for determining the presence of recent /late viral infections,

## SARS-CoV 2 Structure

Spike (S1 & S2)

Nucleocapsid (N)

Membrane (M)

Envelope (E)

ssRNA
(+ sense, ~30kb in length)

Angiotensin Converting
Enzyme-2 Receptor

Receptor Binding Domain

**Fig. 1**: SARS-CoV-2 structure, with representation of the virulence spike structure, and the Angiotensin Converting Enzyme II Receptor (ACE2 receptor)

giving results within 2 days (Chhikara *et al*., 2020). c)-Computed Tomography scan (CT-scan), which provides until now the most helpful tool for COVID-19 diagnosis (Salehi *et al*., 2020). Typical features of the CT initially include bilateral multi-lobar ground-glass opacities, with a peripheral, asymmetric and posterior distribution. Elaine *et al*., (2020) added that the sub-pleural dominance, crazy paving, and consolidation may develop as the disease evolves.

## 5. Vaccine development

A study conducted by Barrett *et al*., (2009) defined vaccination as a biological procedure that provide an active acquired immunity against a particular infectious disease. Bardiya and Bae, (2005) reported that vaccination as a medical process considers the most effective prophylactic method for preventing the infectious diseases. According to Plotkin, (2005), there are 7 main types of vaccines: 1) live attenuated vaccine, 2) inactivated vaccine, 3) subunit (Liljeqvist and Ståhl, 1999) or recombinant protein vaccine (Cox, 2012), 4) polysaccharide vaccine, 5) toxoid vaccine, 6) RNA/mRNA vaccine (Kreiter *et al*., 2011), and 7) DNA Vaccine (Liu, 2003). All mechanisms of vaccination depend upon stimulating the immune-response to recognize a threat, destroy it, form memorial immunity against the foreign agent, and

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then supply the body with an efficient prophylaxis against this wild type of infection.

Up till now no vaccine has been established for COVID-19, but there are multiple attempts in progress to develop it. Best opinions said that no COVID-19 vaccine will be available before January, 2021. Only two vaccine development projects are now under clinical evaluation; one of them is located in the United States of America (USA) and is managed by Moderna Corporation, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) using RNA platform (Moderna Co. 2020). This project is funded by the Coalition for Epidemic Preparedness (CEPI. 2020), phase 1 of this clinical trial started at March, 2020, and ends at June, 2021. On the other hand, the other project is performed by the CanSino Biologics and Beijing Institute of Biotechnology, in China, depending on the non-replicating viral vector for producing the vaccine. This project is supposed to finish its phase I at the end of December, 2020.

At the same time, there are another 79 vaccine production trails states in their preclinical phases, varying in vaccine platform production between DNA, RNA, S protein and\or protein subunit (Le *et al*., 2020).

## 6. Treatment trials

Rapid spread of COVID-19 infection made scientists in front of a single choice, which is to investigate the existing drugs already in the market for possible new therapeutic purposes for COVID-19 that is named as "Drug Repositioning" Fig. (2). A new drug discovery passes through; drug design, molecular docking, chemical synthesis, trials on animals then human ending with evaluation and validation from known international associations around the world such as the WHO and the U.S Food and Drug Administration (FDA). Thus, interventions are likely to require months or even years to develop.

Several existing antiviral medications that developed previously and\or used as treatments for several diseases including; Severe Acute Respiratory Syndrome (SARS-CoV1), Middle East Respiratory Syndrome (MERS) (Guangdi and De Clercq, 2020), hepatitis B virus (HBV), hepatitis C virus (HCV), influenza virus (Zumla *et al*, 2016), malaria and HIV/AIDS, are being researched for COVID-19 treatments, and are jumping into clinical trials after few in silico studies (Guangdi and De Clercq, 2020).

The drug repositioning trials may be classified as follow:

### a)-Chloroquine

According to Savarino *et al*., (2006); Yan *et al*., (2013); Wang *et al*., (2020), Chloroquine is a widely-used anti-malarial and autoimmune disease drug, which has recently been reported as a potential broad-spectrum antiviral drug. Recently, Cortegiani *et al*., (2020) reported that Chloroquine is known to block the viral infection by increasing the endosomal pH required for virus/cell fusion, as well as by interfering with the glycosylation of cellular receptors of SARS-CoV-1. A recent study conducted by Wang *et al*., (2020) revealed that the effective concentration (EC50) value of chloroquine against SARS-CoV-2 (COVID-19) in Vero E6 cells is $6.90\,\mu M$, which could be clinically achieved on being demonstrated into the plasma of the rheumatoid arthritis patients, who receive 500 mg as administration per day. Chloroquine is a cheap and safe medication that has been used for more than 70 years, thus could be potentially applicable clinically against the SARS-CoV-2 (COVID-19).

### b)-Hydroxychloroquine (analog of Chloroquine)

A recent French study of Gautret *et al*., (2020) was carried out on SARS-CoV-2 (COVID-19) positive patients through receiving 600 mg of hydroxychloroquine daily, and then the viral load in the nasopharyngeal swabs was tested daily in a hospital.
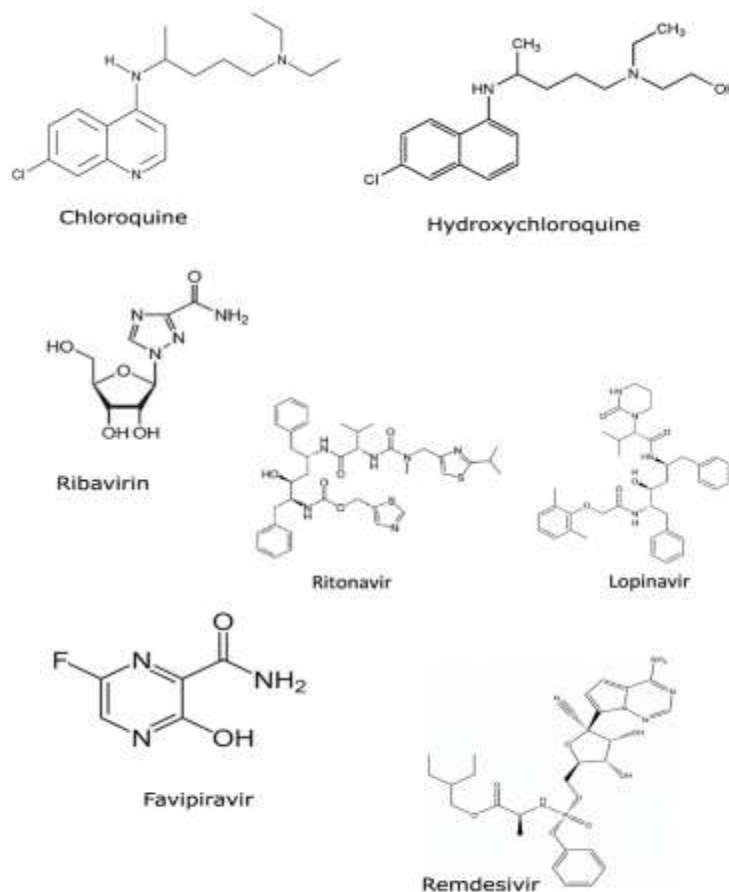
**Fig. 2:** The chemical structure of various medications currently tested for COVID-19 treatments such as; a) Chloroquine, and its analogue b) Hydroxychloroquine, c) Ribavirin, d) Lopinavir/Ritonavir, e) Favipiravir and f) Remdesivir

Results showed that hydroxychloroquine treatment was significantly associated with viral load reduction/disappearance in patients, and its effect was reinforced by association with azithromycin. A study carried out by Biot *et al*., (2006) demonstrated that hydroxychloroquine has an in vitro anti-SARS-CoV activity. In addition, a recent Chinese study of Yao *et al*., (2020) showed that hydroxychloroquine inhibits SARS-CoV-2 *in vitro* with effective concentration (EC50) = 0.72% µM. Hydroxychloroquine showed clinical safety profile better than that of Chloroquine, and allowed higher

daily dose particularly during long-term use, with obvious concerns about drug-drug interactions (Marmor *et al*., 2002).

**c)-Interferon α (IFN-α)**

The Interferon α (IFN-α) is a broad-spectrum antiviral protein that is usually used to treat hepatitis, though it is reported to inhibit SARS-CoV reproduction in vitro (Stockman *et al*., 2006). Administration of IFN-α is through vapor inhalation

at a dose of 5 million units for adults, and 2 times/ day for COVID-19 patients.

### d)-Lopinavir/Ritonavir

Dong *et al*., (2020) revealed that Lopinavir/Ritonavir is a medication for the human immunodeficiency virus (HIV), used in combination with other medications to treat adults and children over 14 days of age, who are infected with HIV-1. The dosage of Lopinavir/Ritonavir permitted for COVID-19 patients is 400 mg/ 100 for adults, 2 times/ day.

### e)-Ribavirin

Ribavirin is a nucleoside analogue with a broad-spectrum of antiviral activities. It is recommended for COVID-19 treatment according to Chinese $7^{th}$ edition guidelines, and is administered intravenously at a dose of 500 mg for adults, 2- 3 times/ day, in combination with IFN-α or Lopinavir/Ritonavir (Dong *et al*., 2020).

### f)-Favipiravir

Du and Chen, (2020) reported that this drug is sold under the brand name Avigan, and is used for treating influenza in Japan since 2014. Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor, where SARS-CoV-2 depends on it for replication inside the host cell. A recent study conducted by Delang *et al*., (2018) revealed that in addition to its anti-influenza virus activity, Favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses. It is converted inside the cells into an active phospho-ribosylated form (Favipiravir-RTP), and is recognized as a substrate by the viral RNA polymerase, thus inhibiting the RNA polymerase activity (Furuta *et al*., 2017).

On the $14^{th}$, February, 2020, a clinical trial was made on Favipiravir by the National Clinical Medical Research Center for Infectious Diseases, at The Third People's Hospital of Shenzhen in China,

for treatment of (SARS-CoV-2) COVID-19, and achieved promising results. Results from a total of 80 patients (including the experimental group and the control group) indicated that Favipiravir had more potent antiviral action than that of Lopinavir/Ritonavir, with no significant adverse reactions on the treated group (Dong *et al*., 2020).

### g)-Remdesivir

Remdesivir is a novel antiviral drug in the class of nucleotide analogs (Adenosine analogue), and is a broad-spectrum antiviral. Wang *et al*., (2020) found that Remdesivir potently blocks SARS-CoV-2 infection at low micro-molar concentrations when tested *in vitro*, with half-maximal effective concentration (EC50) of 0.77 μM. In order to evaluate the efficacy and safety of this drug in COVID-19 patients, a phase III clinical trial was launched on the $5^{th}$ of February, 2020 in China (Zhao *et al*., 2020). Patients in the experimental group received an initial dose of 200 mg of Remdesivir and a subsequent dose of 100 mg for 9 consecutive days via intravenous infusion, in addition to the routine treatment. However, patients in the control group received routine treatment and the same dose of a placebo. Results of this trial are expected to be concluded by the end of April, 2020.

### h)-Ivermectin

Panahi *et al*., (2015) demonstrated that Ivermectin drug is an old medication used to treat many types of parasite infestations such as; head lice, scabies, river blindness, ascariasis, and lymphatic filariasis in the $17^{th}$ of the last century. It can be taken through the mouth, or applied to the skin for external infestations. Recently, a new research conducted by Caly *et al*., (2020) revealed that Ivermectin has a strong antiviral effect against SARS-CoV-2, by causing in vitro inhibition of the viral replication (in monkey kidney cell culture "VERO Cells"), with an IC50 of 2.2- 2.8 μM. These results make this drug as a possible candidate for COVID-19 drug repurposing research; however

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authors of this work think Ivermectin needs more studies to assure its exact action on the COVID-19 virus.

### i)-Tocilizumab

Interleukin 6 (IL-6) is a cytokine that plays an important role in human immune response, and is implicated in the pathogenesis of many diseases. Tocilizumab is developed by Hoffmann–La Roche and Chugai companies. It is an immunosuppressive drug, used mainly for treatment of the rheumatoid arthritis (RA) and the systemic juvenile idiopathic arthritis (Venkiteshwaran, 2009). Moreover, Tocilizumab is a humanized monoclonal antibody against the Interleukin-6 receptor (IL-6R). Jones *et al*., (2010) reported that Tocilizumab binds to the soluble as well as to the membrane bound Interleukin-6 receptors, thus hindering IL-6 from exerting its pro-inflammatory effect. In March 2020, China and Italy approved Tocilizumab for treatment of the inflammation in patients with the coronavirus SARS-CoV-2. However, till now there is no evidence about effectiveness of this treatment.

## Conclusion

As the epidemic spreads, scientists around the world are actively exploring drugs that would be potentially effective in combating COVID-19. All Stakeholders try to find a solution for this worldwide crisis. To find and develop a suitable vaccine, it needs too much time in addition to several preclinical and clinical trials, followed by governmental and organizational licensing. That's which directs the decision makers who face this crisis to use medications already found in the market, hoping to have a therapeutic effect on patients with COVID-19 through all stages of the infection.

## Conflict of interest

No conflict of interests exists between the authors of this study.

## Funding source

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