Scientific Research Publishing

Advances in Infectious Diseases, 2020, 10, 16-28
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

The COVID-19 Pandemic: Theories to Therapies

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How to cite this paper: Acharya, S. (2020) The COVID-19 Pandemic: Theories to Therapies. *Advances in Infectious Diseases*, **10**, 16-28.
https://doi.org/10.4236/aid.2020.103003

Received: April 28, 2020
Accepted: May 24, 2020
Published: May 27, 2020

Abstract

Present COVID-19 pandemic has confronted almost every sector of the world creating terrible havoc and impacting day to day life of each individual. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), identified and reported in Wuhan city, China spread across the globe with an unseen and unpredictable trajectory and limited knowledge of pathogenicity and epidemiology. With the major challenge lying in treatment and vaccine development, researchers and health care workers have come upfront to contribute in terms of knowledge and support. This review presents an overview of the structure, multiplication, and uniqueness of the novel coronavirus focusing on the ongoing treatments and scope of vaccines based on the current studies available in the literature.

Keywords

Infectious Disease, Coronavirus, Pandemic, Vaccine

1. Introduction

Time and again there are reports of new viruses emerging, be it a new species from the laboratory (H1N1) or new viruses discovered or transmitted from animals (MERS, SARS). Table 1 represents the worst events of pandemic in history to date. The recent outbreak of coronavirus (corona in Latin means crown) is one such example, reported in Wuhan city, Hubei Province, China in December 2019 [1] [2]. Epidemiological reports suggest that the Wuhan virus, as largely said was associated with a Huanan seafood market in Wuhan. The very first case reported (a 41-year-old worker at the seafood market) was admitted to hospital on Dec 12, 2019, with a complaint of unproductive cough, fever, weakness, and chest ache. Meta-transcriptomic sequencing of bronchoalveolar lavage (BAL) fluid from another patient revealed the presence of a novel single stranded RNA virus strain (29,903 nucleotides) from the family *Coronaviridae* [3]. Since then,

the virus is known to have multiple names like SARS-CoV-2 [4] and HCoV-19 [5] and the outbreak as COVID-19 (coronavirus disease 2019). Phylogenetic analysis of whole genome (~29.9 kb) revealed that the novel virus is strikingly similar to a SARS-like coronavirus with a percentage match of 89.1 [3] indicating a zoonotic transfer from animal precisely bats sold at the wet market in Wuhan (**Figure 1(a)** and **Figure 1(b)**). But the fact that there were no bats present in the Huanan seafood market is drawing the attention of several researchers hinting at the virus to be lab-made.

Also, to substantiate, there are some reports claiming patients as early as November 17th (which needs validation) and December 1st which had no direct connection to the wet market, and no epidemiologist link to the later cases [6]. Investigations are ongoing throughout the world to trace the actual time of origin and its spread. As of now, there has been a report of 4 million cases of infection and 280,965 deaths in this global pandemic affecting 211 countries within four months. Current review provides an insight into the origin of the novel coronavirus-SARS-CoV2 and its distinctive features highlighting the multiplication and phenomenal spread.

2. Theories of Origin

All the coronaviruses infecting humans have animal origins like bats, rodents, or camels. The last outbreak of SARS in 2002-03 and MERS in 2012 are the results of zoonotic transfers across the species barrier which were considered highly

Table 1. Representing major pandemic outbreaks in the history.

Name	Major Symptoms	First Detection	Global Cases	Global Death Rate	Transmission	Affected groups	Treatments	Vaccines	End of Pandemic
1918 Influenza	fever, nausea, aches, diarrhea	March 1918, NA	500 million	nearly 2%	respiratory droplets	ages 20 - 40	none	none	summer 1919
Seasonal Flu	fever, sore throat, cough, fatigue	NA	1 billion	0.10%	respiratory droplets	older adults and immuno-compromised	Tamiflu, Relenza, Rapivab, Xofluza	available	NA
2002-2004 SARS	fever, cough, malaise	November 2002, China	8098	15%	respiratory droplets and contaminated surfaces	older individual >60 had higher death rate	antivirals and steroids	available	July 2003
H1N1 Flu Pandemic	fever, chills, cough, body ache	2009, Mexico and US	60.8 million U.S cases	0.02%	respiratory droplets	children between 5 - 19	antivirals	available	August 2010
Ebola	fever, aches, pain, diarrhea, weakness, vomiting	2013, Guinea	28,652	50%	bodily fluids like blood, sweat, feces and close contact	children	none	none	March 2016
COVID-19	unproductive cough, fever, shortness of breath, headache	December 2019, China	>4 million	3.40%	unproductive cough, fever, shortness of breath, headache	adults over 60 and with underlying health conditions	none	none	NA

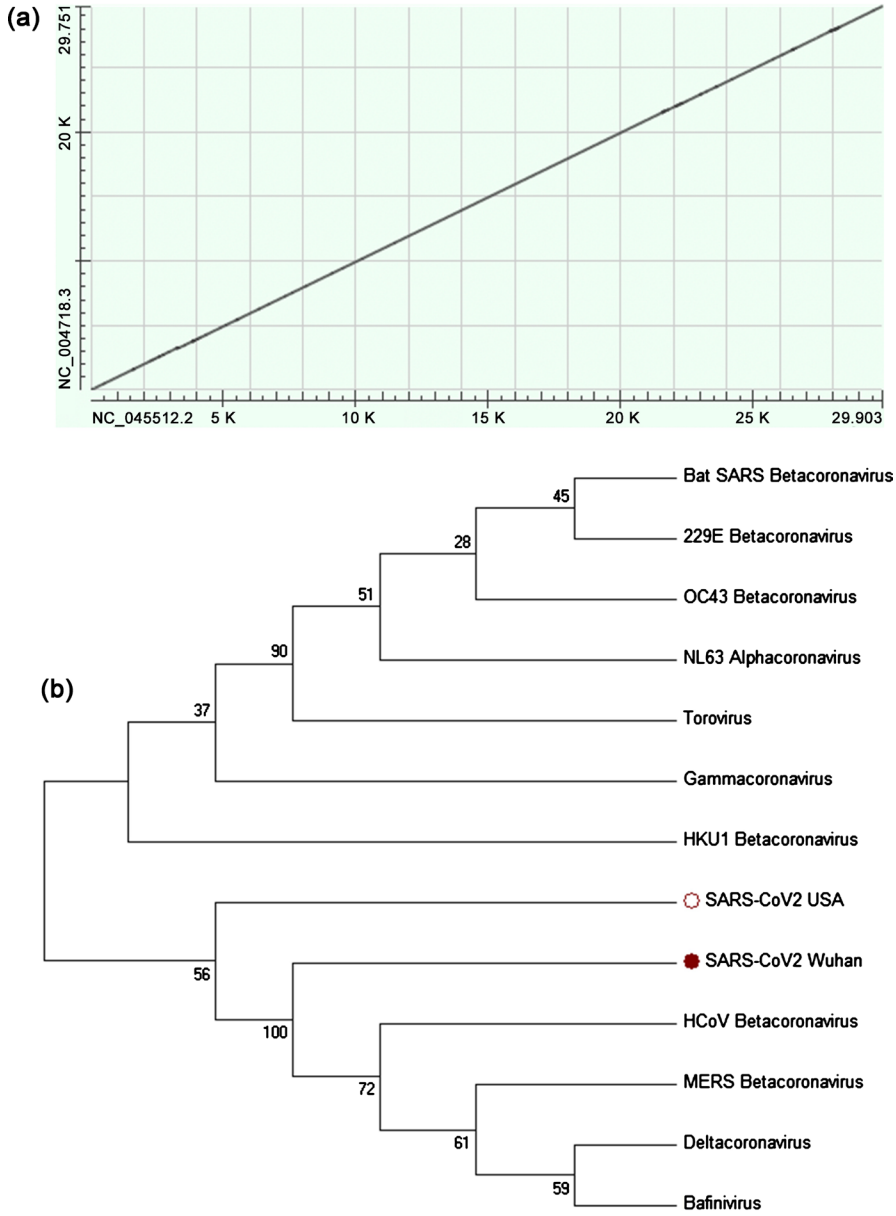

Figure 1. Dot Blast between novel coronavirus (NC_045512.2) and existing SARS-like coronavirus (NC_0047183) showing 89.1% match (Source: NCBI). (b) Maximum Parsimony analysis of taxa using MEGA6 software positions SARS-CoV2 very closely to the human coronaviruses. The bootstrap consensus tree inferred from 100 replicates is taken to represent the evolutionary history of the taxa analyzed. Branches corresponding to partitions reproduced in less than 50% bootstrap replicates are collapsed.

pathogenic. Some theories suggest natural selection in humans [7] and the other way as natural selection in animals before zoonotic transfer with respect to the origin of novel coronavirus [8]. SARS-CoV2 is thought to be originated from bat with an intermediate host-pangolin before infecting humans [8]. Although genomic features of SARS-CoV are identical to *Rhinolophus affinis* (bat), the differences lie in the viral binding sites that share close similarity with the Malayan pangolins (*Manis javanica*) indicating a natural selection before human trans-

mission [9]. With a common ancestor and an intermediate host, the chances are high that the SARS-CoV2 might have jumped to humans and prevailing in there before infecting a cluster [9]. Since the 2002-03 SARS outbreak, research on coronaviruses has drastically increased. There are reports of laboratory escape of SARS-CoV that might be another angle to look at [10]. More research and scientific transparency in this field is the need of the hour.

3. Classification and Structure of Coronavirus

Coronavirus belongs to the order *Nidovirales* and family *Coronaviridae* that divides into two sub-family namely *Coronavirinae* and *Torovirinae*. The *Coronavirinae* is further divided into a group of four—alpha, beta, gamma, and delta. SARS-CoV2, a beta coronavirus is the seventh known coronavirus that infects humans and causes severe pneumonia-like disease along with SARS-CoV and MERS-CoV (**Figure 2**). The alpha coronaviruses like HCoV-229E and HCoV-NL63 are known to show only minimal symptoms in humans [11].

All the viruses classified under this order are enveloped and have a positive non-segmented RNA genome of ~30 kb. The presence of 5' cap structure and poly A tail allows the virus to act like mRNA for translation. The genome organization of coronavirus is described as 5'-UTR-replicase-Spike (S)-Envelope (E)-Membrane (M)-Nucleocapsid (N)-3'UTR-polyA tail (**Figure 3**). Structural proteins are essential for infection and viral assembly whereas genes coding for non-structural proteins seems to have a minor role in the replication in tissue culture while some have very important roles in pathogenesis [12] [13]. The spike comprises of two subunits-S1 and S2 which is 1285 amino acids long [9]. The receptor binding domain (RBD) is located in the S1 subunit that binds to ACE2 (angiotensin-converting enzyme 2) of human cells and triggers a cascade of inflammation in the respiratory tract [13] [14] [15]. ACE2 is an ectoenzyme that converts angiotension II to angiotension 1 - 7, a key regulator of blood pressure angiotensin-converting enzyme [16].

4. What's New in SARS-CoV2?

The densely glycosylated spike protein is a fusion protein (trimeric class I) that

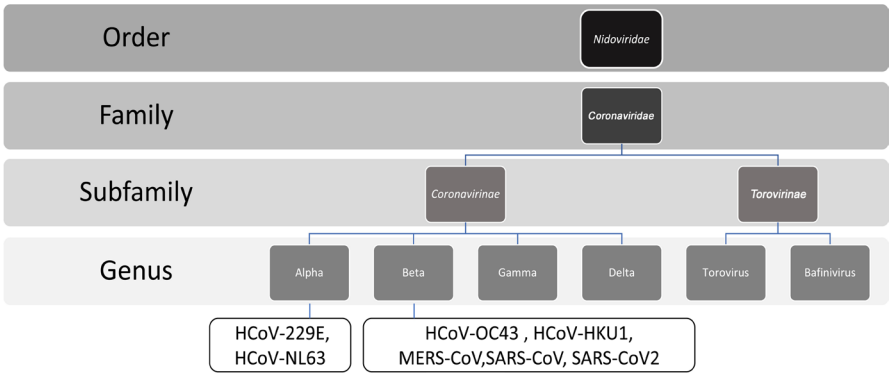

Figure 2. Classification of coronavirus.

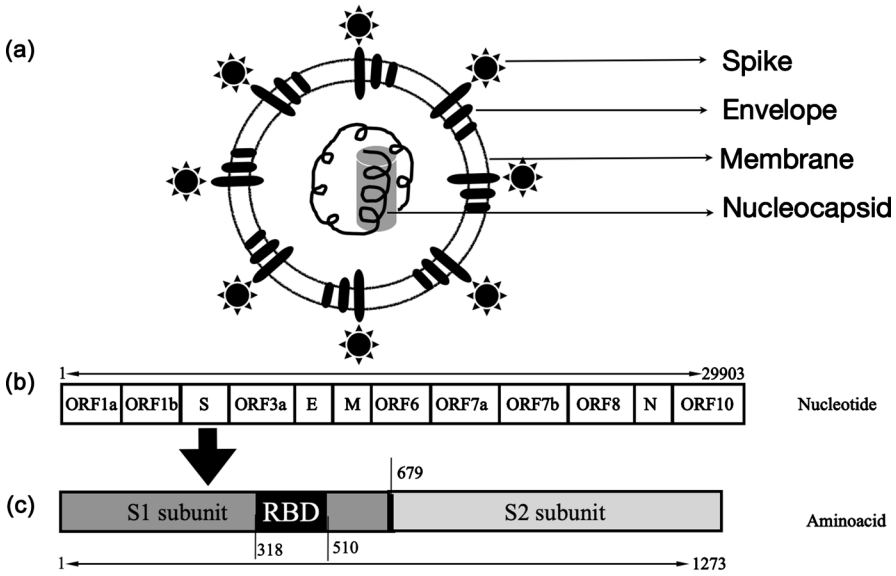

Figure 3. Structure (a), genetic organization (b), and corresponding peptide sequence (c) of coronavirus.

changes its confrontation and undergoes a structural rearrangement to enter into the target cell. The entire process begins when the S1 subunit binds to the receptor which leads to its destabilization and shedding of the subunit. This lets the stabilization of S2 subunit post fusion. According to Wrapp *et al.*, these two states are referred to as "down and up" confrontation, where down is the receptor remote state and the later referred to as receptor ready state which is comparatively less stable. Biophysical assays made by Wrapp *et al.*, indicates that the spike protein binds to the host cell ten times stronger than other SARS viruses. Maybe that's the reason the SARS-CoV2 spreads so fast from person to person through respiratory transmission. The spike protein hence is the potential candidate for vaccine design and development [17]. The RBD essentially is the key element for binding and is the most adaptable fragment of the coronavirus family. Five out of six critical amino acids seemed to be different than the existing SARS-CoV that results in the high affinity binding to the host cell receptor [9]. Anderson *et al.*, suggests the presence of polybasic cleavage site at S1/S2 junction allowing proper cleavage by proteases thereby indicating superior host selection and infection [9].

5. Entry and Replication of Coronaviruses

As the spike protein binds to the ACE2 receptor of the target cell, it unlocks its way into the host cell cytoplasm (**Figure 4**). The entry into the host cell is facilitated when TMPRSS2 (type 2 transmembrane protease) chops off the ACE2 thereby activating the spike protein, a mechanism followed by the influenza virus [18].

After entry, the virus unwraps the envelope or the E protein, thereby letting the nuclear content or the genomic RNA release in the cytosol. The ORF1a and

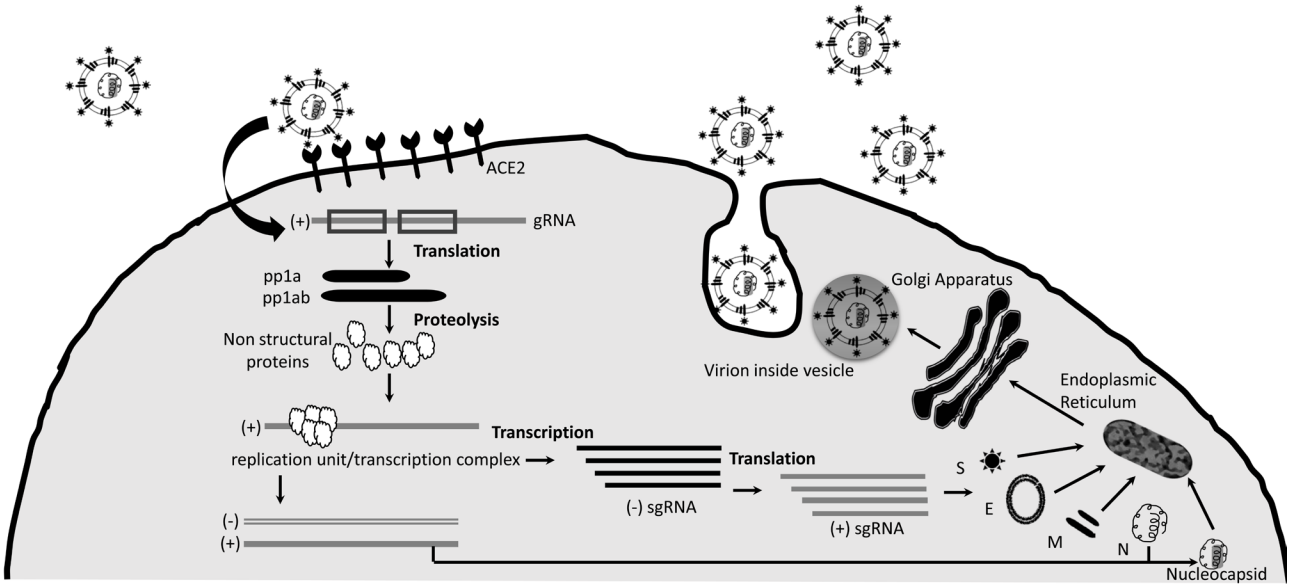

Figure 4. Schematic representation of virus entry and release in the host cytoplasm.

ORF1b translate into pp1a and pp1ab proteins respectively. Proteases cleave of these proteins to generate 16 non-structural proteins essential for new virus assembly. Some of them form transcription complex/replication unit-RNA-dependent RNA polymerase, RdRp, that uses the [+] strand gRNA as the template to make copies. The replicated [+] strand is now the genome of a new virus particle. Subgenomic RNAs are translated into structural proteins-S, E, M, and N proteins that form the viral particle out of which the first three enters the endoplasmic reticulum (ER) and the last one, with the [+] strand gRNA becomes a nucleoprotein complex. Inside the ER-Golgi apparatus complex, the proteins amalgamate into a new virus unit which then is excreted out to the extracellular space with the help of vesicle (Figure 4).

6. Pathogenicity, Incubation Period and Transmission Rate of COVID-19

The pandemic has taken over two hundred thousand lives affecting almost every part of the globe. New cases and causalities are reported every day and still, there is no sign of relief. SARS-CoV2 that causes atypical pneumonia-like disease and sometimes acute respiratory distress syndrome (ARDS) especially in the lower respiratory tract binds to the ACE2 receptor of host cells resulting in rapid respiratory failure. These receptors are present in the epithelial cells of the upper respiratory tract, alveoli, trachea, bronchi and bronchial serous glands [19] as well as macrophages and alveolar monocytes. They serve as the primary target where the virus enters, replicate, and release in huge numbers. The presence of ACE2 in endothelial cells of arteries and veins, mucosal linings of the intestines, epithelial cells of the kidney and renal tubes, and immune cells make them secondary target infecting almost the entire body. That is the reason a person is completely isolated as there are high chances of presence of virions in patients'

saliva, sweat, urine, and stool.

The presence of ACE2 is still not the determining factor of vulnerability, though it can be speculated that higher the receptor higher the risk factor. Studies have confirmed the involvement of ACE2 in diabetes, cardiac function, and hypertension [20] [21] [22]. Hence, people associated with any of these ailments fall into the category of serious illness and death. Elderly people are also at elevated risk because of a reduced immune response, multiple prevailing diseases, and altered physiological changes associated with aging. But the norm "only elderly people are at high risk" is solely wrong. As per WHO, 10% - 15% of cases reported are under the age of 50 and have moderate to very severe infection leading to death. Statistics suggest that the COVID-19 has a brief incubation period but a lengthier clinical course as patients take a long time to either recover or die [23]. It is estimated that the median incubation period for this virus is around 5.1 days [24]. That means it is mostly the 5^{th} day when a person with coronavirus infection starts to show symptoms after exposure, in other words, it become symptomatic. Though, the range varies from day 1 to day 14. Other respiratory illnesses caused by the coronavirus family also have a similar incubation period—SARS has a mean of 5 days with range 2 to 14 days [25]. Similarly, MERS [26] has a mean of 5 to 7 days and range 2 to 14 days whereas, non-SARS human coronavirus has a mean of 3 days ranging from 2 to 5 days [27]. Preliminary analysis suggests that the transmission rate or the reproduction number stated as R_0 (R naught) in SARS-CoV2 is around 2.24 - 3.58 which means a single infected person can infect 2 - 4 people. Whereas in the case of SARS (1 - 2.75) and MERS (>1), R_0 is comparatively low [18] [28]. It is very important to have the exact knowledge of the incubation period and the rate of transmission to slow down the spread and also to safeguard the use of protective gear in the hospitals amidst the acute shortage.

7. Treatments

With the exponential increase of cases and causalities every day, researchers and health officials are trying their best to cope and come up with a possible "treatment". Right now, the best treatment offered is care and intensive support. Preventing the transmission and slowing down the spread by social distancing are the two major goals that are put forth. Clinicians are applying what they know from previous endemics like SARS, MERS, and Ebola. Though similar, COVID-19 is quite different from the previous diseases, hence treating a new disease with old medicine is not giving a satisfactory response. **Table 2** shows the current list of medications that is categorized into host cell based and virus-based delivery. Drugs from various classes like nucleoside analogs, protease inhibitors, host-targeted, and interferons have been tested for the treatment of COVID-19 out of some are already in clinical trials [29].

7.1. Nucleoside Analogs

Nucleoside analog target RNA-dependent RNA polymerase to inhibit replication

Table 2. List of medication in current use for the treatment of COVID-19.

Drugs	Mechanism of action
Virus-based approaches	
Remdesvir	Terminates premature viral chain
Galidesvir	Terminates premature viral chain
Favipiravir	Inhibits RdRp
Ribavirin	Inhibits viral RNA synthesis
Penciclovir	Inhibits RdRp
Nafamostat	Inhibits entry
Griffithsin	Inhibits entry
Lopinavir	Decreases viral load
Ritonavir	Increases the bio-availability of ritonavir
Darunavir	Prevents viral replication
camostat mesylate	Blocks TMPRSS2
ASC09F	Decreases viral load
Host-based approaches	
Recombinant interferons	Exogenous interferons
Chloroquine	Blocks viral entry
Nitazoxanide	Induces host innate immune response
Tocilizumab	Suppresses host immunity
Interferon-I	Modulates immune response
Glucocorticoids	Inhibit cytokine production

in broad-spectrum of viruses. Remdesivir and galidesivir, two experimental adenosine analog that leads to pre-mature termination of viral chains thereby inhibiting RNA synthesis demonstrates antiviral activity [30]. Remdesivir which is under clinical development for the treatment of Ebola is showing promising results. Studies confirm that remdesivir is effective in the control of SARS-CoV2 infection *in vitro*. National Institute of Health (NIH) has already started clinical trials to treat COVID-19. Ribavirin and favipiravir, two approved drugs for hepatitis C virus (HCV) and respiratory syncytial virus (RSV) were evaluated against SARS-CoV2 but the efficacy is uncertain.

7.2. Protease Inhibitors

Lopinavir and ritonavir having antiviral activity against human coronaviruses are used as a combination drug for the treatment of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Open trials on COVID-19 positive patients showed no improvement suggesting further investigation. Other protease inhibitors like nafamostat and griffithsin showed to inhibit glycosylation of spike protein of coronaviruses [31]. Hoffman *et al*., have clinically shown, camostat mesylate, a serine protease inhibitor which blocks

TMPRSS2 activity could be considered a potential drug to treat COVID-19 [31]. Currently, this drug has been approved in Japan for human intake [32] [33].

7.3. Host-Based

Chloroquine and hydroxychloroquine that is in use since the last 70 years as front-line medication for malaria is the next drug candidate. They restrict the glycosylation of spike protein with the ACE2 receptor [34] [35]. It also increases the endosomal pH required for viral fusion to the cell thereby blocking the entry into the target cells [31]. Li and De Clerq have recently demonstrated that nitazoxanide and ribavirin show inhibitory action against SARS-CoV2 [29].

7.4. Interferons, Antibodies and Corticosteroids

Tocilizumab, an immune-suppressor used to treat rheumatoid arthritis and juvenile chronic arthritis is currently one of the popular drugs with some success [36]. It has been observed that critical COVID-19 patients experience a cytokine storm resulting in ARDS and subsequently death. Tocilizumab is a humanized monoclonal antibody against IL-6. Sallard *et al.*, in their review have suggested the use of Type I interferon (IFN-I) as a possible treatment for COVID-19 patients [37]. IFN-I are a group of cytokines that have a broad range of antiviral activity *in vitro* and are currently under clinical trial for the treatment of MERS-CoV and SARS-CoV patients. As there is a striking similarity between coronaviruses, IFN-I could be considered a potential drug and can be given to the patients in their early phase of infection [38]. Glucocorticoids, the primary medication in the previous endemic of SARS and MERS have also been listed for COVID-19 patients.

Beside available drugs, clinicians are using convalescent plasma to treat the novel coronavirus patients which means serum from recovered patients carrying vital antibodies is administered into newly infected patients. This neutralizes the virus thereby reducing the viral load and further complication. Though this modality was already in use during the Ebola outbreak (2014-15) but seems to be highly effective at the present condition. However, the amount of serum available currently is essentially very low as the number of new cases is far more than the number of recovered patients.

8. Vaccines

The development of a vaccine for COVID-19 at this time is the ultimate aim of all the SARS-CoV2 researchers throughout the world. With the knowledge and experience of past SARS and MERS outbreaks and recent mapping of SARS-CoV2 virus [17], scientists have started clinical trials to deliver a successful candidate that could neutralize the deadly virus. According to WHO, there are about 83 potential candidate vaccines out of which 77 are in pre-clinical trials, 5 in phase 1 and 1 in phase 2 clinical trial (**Table 3**).

While there are effective traditional methods of vaccine development (live

Table 3. Current status of vaccine development (Source: WHO).

Developer	Country	Clinical Trial Phase	Strategy
CanSino Biological Inc./Beijing Institute of Biotechnology	China	I and II	Non-replicating viral vector
Beijing Institute of Biological Products/ Wuhan Institute of Biological Products	China	I	Inactivated virus
Sinovac	China	I	Inactivated virus
University of Oxford	UK	I	Non-Replicating Viral Vector
BioNTech/Fosun Pharma/Pfizer	USA	I	RNA
Moderna/NIAID	USA	I	RNA
Inovio Pharmaceutical	USA	I	DNA

attenuated, inactivated, subunit and toxoids vaccines) relatively newer techniques (RNA or DNA based) have gained popularity as they are less expensive and rapid which is quite crucial in times of pandemic like this [39] [40] [41] [42]. Potential candidates for SARS-CoV2 vaccines include—the spike protein, the RBD, and the inactivated virus. The inactivated virus can be considered as the first-generation vaccines as they contain various structural proteins to induce neutralizing antibodies but the risk and safety concerns of investigators are higher. Incomplete or partial activation may pose a serious risk of infection or might even cause another SARS-like disease by inducing harmful inflammatory responses [43]. Recombinant vector-based vaccines expressing the S protein/RBD might produce neutralizing antibodies with a possible inhibition of viral binding and fusion to the host cell. According to a recent finding by Walls *et al*., SARS-CoV polyclonal antibodies inhibited the spike-mediated entry of SARS-CoV2 into VeroE6 cells [44]. With all potential and capabilities, the vaccine industry is working overtime to deliver and scale up a successful candidate.

Acknowledgements

The author would like to acknowledge Dr. Indu B. Maiti for his guidance and support. SA would like to thank Dr. Moonmoon Das for assistance in designing the phylogenetic tree.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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