COVID-19 Threat to the World: Current and Possible Diagnostic/Treatment Strategies

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ABSTRACT: The outbreak of coronavirus disease 2019 (COVID-19) has resulted in a world-wide crisis. To contain the virus, it is important to find infected individuals and isolate them to stop transmission. Various diagnostic techniques are used to check for infection. With the havoc that severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) has created, it is imperative to work on alternative diagnostic techniques that can be used at both point of care with little or no expertise and at mass testing (i.e., when screening). Despite extensive research, to this date no specific effective treatment or cure is available to neutralize this viral infection. Globally, researchers are working to develop effective treatments, and several vaccines have been approved for public use. We found the studies that we explored for this review using appropriate key words for indexing in PubMed and Google Scholar from 2019 to 2020. We compile various techniques that have been used worldwide to diagnose and treat SARS-CoV-2 and discuss novel methods that may be modified for use in diagnosis and treatment. It is crucial to develop a more specific serological test for diagnosis that can rule out the possibility of COVID-19 and be used for mass testing. An affordable, safe, targeted, effective treatment must be developed to cure this disease, which has created a public health emergency of international concern.

KEY WORDS: COVID-19, SARS-CoV-2, diagnosis, qRT-PCR, viral infection, pandemic, public health

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is critical respiratory illness caused by severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2), a member of the family of coronaviruses.[1] SARS-CoV-2 has genetic similarity to SARS-CoV, Middle-East respiratory syndrome (MERS)-CoV, and other coronaviruses (see Table 1). Phylogenetic evidence suggests that SARS-CoV-2 belongs to the genus *Betacoronavirus*. A likely carrier for SARS-CoV-2 is the bat.[7]

The initial outbreak of disease occurred in the Wuhan province of China. The World Health Organization (WHO) reports that through January 20, 2021, the virus has affected more than 90 million people and has caused death to more than 2 million globally in 213 countries.[1] The worst affected regions are America, Europe, and the eastern Mediterranean, and worst affected countries are the United States (US), Brazil, Russia, the United Kingdom (UK), Spain, Italy, Germany, Turkey, India, France, Iran, and Peru, with more than 30 million cases.[1] Demographically, the COVID-19 mortality rate is

comparatively higher among those who are older than 60 yr, as seen in China, Italy, and South Korea.[8] Not just advanced age but also comorbidities present in COVID-19 patients. Those with underlying conditions such as diabetes, hypertension, and other respiratory and cardiovascular diseases are likelier to develop severe cases compared to patients without these comorbidities.[9,10]

Most COVID-19 transmission occurs person to person via either direct contact or from affected persons' aerosol droplets that become airborne from coughing to through any other physical contact that might lead to exchange of droplets.[7] COVID-19 affects the respiratory pathway with symptoms including fever, cough, fatigue, headache, hemoptysis, diarrhea, dyspnea, and, in severe cases, pneumonia, acute respiratory syndrome, and severe cardiac injury. A recent new strain that emerged in the UK, named SARS-CoV-2 Variant of Concern (VOC) 202012/01, can spread more easily in humans. Because it is a mutated variant, it can evade the older reverse-transcription–polymerase chain reaction (RT-PCR) diagnostic test, according to the Centers

TABLE 1: Types of coronaviruses

Alphacoronavirus	*Betacoronavirus*	Novel
229E Common cold symptoms in adults[2]	OC43; common respiratory disease symptoms[4]	SARS-CoV-2 (novel; SARS causes COVID-19); severe respiratory illness with flu like symptoms[6]
NL63 Lower respiratory tract infection in infants[3]	HKU1; mild respiratory tract infection[5]	
	MERS; severe respiratory illness with flu like symptoms[6]	
	SARS-CoV; severe respiratory Illness with flu like symptoms[6]	

CoV, Covid; COVID, coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

for Disease Control (CDC).[6] The incubation period for the disease, which varies with patient age and degree of immunity, ranges from 2 to 14 d, with an average of 5.2 d.[11]

No specific treatment for COVID-19 exists yet. However, the CDC has issued guidelines for safe medical management of COVID-19 patients. Clinical trials are underway to further substantiate the use of drugs/treatments such as hydroxychloroquine, remdesivir, interleukin inhibitors, and convalescent plasma therapy to treat COVID-19 patients.[12] At present, commonly and extensively used treatment procedures that focus on the famous phrase "prevention is worth a pound of cure" include quarantine, lock down, and travel bans.

The enormously high rate with which the virus has been affecting individuals is worrisome, and its timely diagnosis is imperative to contain the spread. Like other lethal diseases, COVID-19 early diagnosis is crucial but can also present challenges. Currently, of the diagnostic methods used, only a few are accurate, efficient, rapid, and convenient. Methods include recording temperature via infrared thermometer, chest X-ray, chest computed tomography (CT) scan, virus isolation and detection, enzyme-linked immunosorbent assay (ELISA)–based serological test, clustered regularly interspaced short palindromic repeats (CRISPR)–Cas12-based lateral flow assay, and qualitative (q)RT-PCR detection of virus in samples collected from nasopharynx, trachea, and sputum.[13,14] Of these, only qRT-PCR is considered to be the gold standard for COVID-19 diagnosis, although it has limitations.

In this review, we shed light on currently used COVID-19 diagnostic and treatment approaches/tools, their merits/demerits, and possible diagnostic and treatment methods/tools that can provide information about infection rate in a concise way, from a single platform to fight against COVID-19 using a more efficient approach.

II. METHODOLOGY

The research articles explored for the completion of this review were accessed from PubMed and Google Scholar during the years 2019 and 2020. We used appropriate key words for indexing.

A. SARS-CoV-2 Symptoms, Transmission, and Cellular Targets

SARS-CoV-2 is a novel virus that has positive single-stranded RNA containing 29,891 nucleotides and encoding for 9860 amino acids. It belongs to the *Coronaviridae* family and *Coronavirinae* subfamily (order *Nidovirales*).[15,16] Electron microscopy reveals the classic crown-like appearance of this virus, with glycoproteins as spikes on the envelope (the outermost virus layer). Members of this viral family cause respiratory, enteric, hepatic, and neurological infections in animals including camels, cattle, cats, and bats.[9] Chan et al. isolated the new HCoV (human

coronavirus) from a cluster of patients with atypical pneumonia after visiting Wuhan. These investigators found that the HCoV genome has 89% nucleotide uniqueness with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV.[17] This explains why the new virus is termed SARS-CoV-2.

COVID-19 is clinically classified into five major types. The first is asymptomatic/recessive infection, in which a SARS-CoV-2 etiology examination is positive but does not show clinical symptoms. However, CT scans in asymptomatic patients found lesions in peripheral and subpleural lung areas. The second classification is acute upper respiratory tract infection with cough, pharyngeal pain, fever, nasal obstruction, fatigue, headache, myalgia, discomfort, and a CT scan that does not show pneumonia. The third classification is mild pneumonia that may not accompany fever but is supplemented with various respiratory indicators including cough and CT-scan imaging that demonstrates pneumonia appearances but illness does not reach to the severity of pneumonia. The fourth classification is severe pneumonia that shows one of the following situations: (1) increased respiratory rate, (2) oxygen saturation, (3) anoxia, (4) unconsciousness, or (5) trouble in feeding including dehydration symptoms. The fifth classification is critical with one of the following situations, requiring ICU monitoring and treatment: (1) failure of the respiratory system with the need for mechanical ventilation, (2) tremor, and (3) additional organ failure.[18,19] COVID-19 not only affects the lungs but has also been found to cause severe damage to other organs in the body. Given that COVID-19 targets angiotensin converting enzyme (ACE) and ACE2, which are dominantly present in heart, lungs kidney, liver, and the gastrointestinal (GI) tract, it increases the risk of injuries to these organs.

It has also been observed that patients with COVID-19 have heart enlargement.[20] COVID-19 patients have increased levels of cytokine that can lead to atherosclerotic plaque instability and augment risk of myocardial injury and heart failure.[20] The presence of SARS-CoV-2 in urine suggests the possibility of kidney injury. Although data are inconsistent, they suggest acute kidney injury, accompanied by sepsis and shock. Furthermore, many patients report GI symptoms such as nausea, vomiting, and abdominal pain.[20] The reasons why Middle East respiratory syndrome (MERS) and SARS viruses are able to break species barrier (i.e., jump from natural hosts to humans) and result in severe infection in humans are not yet understood. It is believed that the previously identified MERS and SARS viruses initially originated from bats and then moved to humans via transmittance through other mammalian hosts such as the Himalayan palm civet and dromedary camel for SARS-CoV and MERS-CoV, respectively.[16] The exact origin and route of SARS-CoV-2 spread are still unclear, but it is assumed that it originated from an animal species.

Studies have explored that both SARS-CoV-2 and SARS-CoV show identical binding receptors and binding properties. The coronavirus S protein binds to the infected host's receptor protein, permitting virus attack and contamination of host cells.[21,22] Another study demonstrated that ACE2 protein serves as a receptor for S protein together with the support of cellular transmembrane protease, serine 2 (TMPRSS2).[23] ACE2 and TMPRSS2 are indicators for SARS-CoV-2 human infection, and ACE2 is an essential element for SARS-CoV-2 entry into host cells. This may explain the low susceptibility of SARS-CoV-2 in children, due to their inadequate growth and ACE2 protein's role.[18]

Initial cases of COVID-19 were associated with direct contact in the Hunan Seafood wholesale market of Wuhan, China. It was assumed that animal-to-human transmission was the main mechanism of transmission.[16] However, later cases did not follow this route, instead confirming that the virus transmits via human-to-human contact. COVID-19 mainly uses two routes for transmission: respiratory droplets and contact.[18] Additional transmission assumptions were aerosols, fecal-oral course, and mother to infant,[18,24] but primary virus spread is limited to family members, friends, colleagues in close contact, healthcare specialists, and other close acquaintances.[16]

B. COVID-19 Vulnerability

It is assumed that COVID-19 is worse of a life threat for older individuals or those with serious underlying

diseases (such as cardiovascular disease, hypertension, diabetes) compared to young healthy individuals. In a study of pregnant COVID-19 patients, no SARS-CoV-2 infection was found in the neonates.[25] This shows that pregnancy/delivery is unaffected by COVID-19, which raises the question on use of antiviral drugs in pregnant COVID-19 patients in terms of toxicity and viral infection in the neonate. If it is necessary to use the drugs, risks must be measured before doing so.[25]

Patients with preexisting respiratory disease have low mortality rates compare to cardiac and diabetic patients.[26,27] These findings are unpredictable, but they are beneficial in terms of precautionary measures and future research.

A probable connection exists among ACE2 receptors and cardiac disease, diabetes, and hypertension. This must be considered if Covid patients are treated with ACE inhibitors or angiotensin receptor blockers. Enhanced expression of ACE2 receptors in these individuals may account for the high viral load of SARS-CoV-2. Likewise, inhibitors of ACE2 receptors could be an effective synergistic treatment for this subgroup of COVID-19 patients.[26,27]

III. PREEMPTIVE MEASURES

A. Technology and COVID-19

The outbreak of COVID-19 has placed the world in crisis. To resume activities safely at the workplace and other public places, it is imperative that we have a system to recognize and isolate possible viral carriers. To identify possible carriers without going through expensive and time-consuming diagnostic methods, countries have come up with various contact-tracing applications. The UK has National Health Service COVID-19, China the Chinese Health Code system, India has ArogayaSetu, France has StopCovid, Switzerland has SwissCovid, Germany has Corona-Warn App, Singapore has Trace-Together, and many more (Table 2).

All apps work with Bluetooth, Wi-Fi, or both to trace someone who has come in contact with an infected person. App-collected data may be used at the workplace/public locations to rule out

TABLE 2: Applications used to assess infection risk based on individuals' location and those around them

S. Number	Application/software	Country or state
1.	ArogayaSetu	India
2.	WeChat, Alipay, and health code system	China
3.	Stay Home Safe	Honk Kong
4.	Trace Together	Singapore
5.	CovidSafe	Australia
6.	Bluezone	Vietnam
7.	Haamagen	Israel
8.	Corona Data Donation and Corona-Warn	Germany
9.	NHS	United Kingdom
10.	Stopp Corona	Austria
11.	Apple and Google SDK	Europe and United States (some parts)
12.	Healthy Together	Utah, US
13.	Care 19	Dakota, US
14.	ABTracetogether	Alberta, Canada
15.	StopCovid	France
16.	SwissCovid	Switzerland

NHS, National Health Service; SDK, software development kit.

the possibility of infection. However, apps are not completely accurate and efficacy largely depends on the quality of data collected and number of app users.[28,29]

B. Thermal Screening

Every organization/workplace/institution is searching for a new standard operating protocol to resume their activities. To rule out even the slightest possibility of a COVID-19–infected individual at the workplace, use of infrared hand-held noncontact thermometers are used to screen the temperature of individuals because one of the symptoms of COVID-19 is increased body temperature (fever). However, increased body temperature does not necessarily suggest that a person has COVID-19. The human body can develop fever in even the slightest

of infection cases by other causes. Moreover, infrared thermometers are not 100% accurate; they are less sensitive than oral thermometers and their accuracy depends on various parameters such as proximity of thermometer from body part and thermometer handling.[30]

IV. DIAGNOSTIC MEASURES

A. CT Scan

A CT scan produces a digital image of lung based on the measure of attenuation coefficient (i.e., the reduction of X-ray radiation intensity on passage through matter). The scan uses multiple X-rays to form a cross-section or a three-dimensional image of the organ under screening. CT scanning to diagnose acute respiratory distress syndrome (ARDS) began in the mid-1980s.[31]

In the case of COVID-19, CT-scans are used as a preliminary test to screen possible COVID-19 patients. Given that the number of COVID-19 patients is increasing, with new waves and strains coming,

a rapid test mechanism to diagnose and contain infected individuals must be implemented.[32] Compared to qRT-PCR, CT scans take marginal time to yield results. The National Health Commission of the People's Republic of China suggests the CT scan for diagnosing COVID-19.[33] In scans of COVID-19 patients, ground glass opacities and consolidation are two primary findings. A study by Li and Xia suggested the presence of vascular enlargement, ground glass opacities with consolidation, interlobular septal thickening in a crazy-paving manner, and air bronchogram signs.[31] Long et al. found that COVID-19 confirmed patients had lesions in the right and left lower lobes and left upper lobe, and lesions were majorly distributed peripherally.[34] Ground glass opacities with consolidation remains the primary finding in CT scans of COVID-19 patients (Table 3).[31,34]

CT scans are a quicker way to identify patients with ARDS, but ARDS may not be due to COVID-19.[35,36] Hence, a scan can only be used to manage patients until a confirmatory test is performed. A comparison of scans is shown in Table 4.

TABLE 3: Diagnostic techniques used worldwide to diagnose SARS-CoV-2

Test	Novel/conventional	Working sample	Duration time	Advantages	Limitations
CT scan	Conventional		60–90 min	Can be used to diagnose ARD	Cannot rule out SARS-CoV-2
Serological assay	Novel	Blood/sera	15–30 min	Can suggest previous infection	Not 100% accurate; negative results cannot rule out SARS-CoV-2
qRT-PCR	Conventional	Nasal/oral swab	4–6 h	Specific, sensitive, and most accurate for SARS-CoV-2 diagnosis	Expensive: expertise required to perform; cannot be used at point of care. Many resources required, so may be used for mass testing
CRISPR-Cas12/13a; SHERLOCK; DETECTR	Novel		~ 60 min	Specific, sensitive, and rapid; can be used at point of care	Needs modification to be used for SARS-CoV-2; test kits have not been developed (in developmental stages)

ARD, Acute respiratory disorder; CoV, Covid; CRISPR, clustered regularly interspaced short palindromic repeats; CT, computed tomography; DETECTR, DNA endonuclease-targeted CRISPR *trans* reporter; qRT-PCR, qualitative reverse-transcription–polymerase chain reaction; SARS, severe acute respiratory syndrome; SHERLOCK, specific high-sensitivity enzymatic reporter unlocking.

TABLE 4: Qualitative analysis of CT-scan reports of pneumonia caused by COVID-19 versus bacteria

CT scan of COVID-19 patients	CT scan of non-COVID-19 patients with pneumonia
1. Mottling and ground glass opacity in lower and upper right lobes[36] 2. Transverse CT scan: bilateral, multiple, and lobular mottling and ground glass opacity[36]	1. Patchy and mottling shadows[36] 2. Transverse CT scan: mottling shadows and partial ground glass opacity[36]

CT, Computed tomography.

B. Serological Assays

Serological assays are performed to assess antibodies that are formed inside the human body. Immunoglobulin M (IgM) and IgG are two antibodies that are frequently targeted to diagnose infection. IgM antibodies are a sign of acute viral infection and usually disappear after a period of 5–7 d, but IgG stays longer in the bloodstream to fight infection. An antibody or serological test is a faster method for ruling out a viral infection, so its usage and development in diagnosis of COVID-19 is imperative given that infection is spreading at a tremendous rate. Li et al. developed a point-of-care lateral flow immunoassay kit that can be used to detect IgM and IgG in blood.[37] The kit uses two mouse antihuman monoclonal antibodies (IgM and IgG) on a nitrocellulose membrane in the form of two strips and a surface antigen from SARS-CoV-2 that is conjugated with gold on a conjugation membrane that is present before the two strips.[37] The assay mechanism depends on chromatographic lateral flow of the sample across the strip after antibodies. If present, the antibodies adhere to the SARS-CoV-2 antigen in conjugation with a membrane containing the gold colorimetric reagent. This kit was found to be accurate, with 88.66% sensitivity and 90.63% specificity. In other research, Capello et al. suggested the potential of serological testing and developed a rapid test named VivaDiag COVID-19 IgM/IgG Rapid Test.[38] In addition, Guo et al. developed an ELISA-based method to test for the presence of IgM, IgG, and IgA.[39] They verified that in COVID-19, IgM can be detected at the d 5 after infection, and IgG at d14 (both are median days).[39] A similar antibody kit named COVID-19 (IgM, IgG, IgA) MICROLISA was developed (J. Mitra & Co., New Delhi, India).[40] The kit assesses IgA along with IgG and IgM that

increases overall assay sensitivity. The test is also ELISA-based and takes ~ 90 min to complete. In addition to the above-mentioned antibodies, the Indian Council of Medical Research and All India Institute of Medical Sciences, both in New Delhi, India, have approved the use of antigen assay Standard Q COVID-19 Ag detection kit (SD Biosensor, Gyeonggi-do, Korea).[41] This is a rapid chromatographic immunoassay that yields results in ~ 30 min.[41] The use of serological assay along with current standard qRT-PCR can be used to increase accuracy and reduce time in patient diagnosis.

C. CRISPR-Cas–Based Detection

Bacteria uses the CRISPR-Cas system as an immune method to degrade foreign nucleic acid. CRISPR with Cas works to degrade invading nucleic acids in microbes.[42] This system has already been modified for use with humans. With increased frequency of epidemics, researchers explored whether the system could be used as a detection tool at point of care. Two different groups came up with DETECTR (DNA endonuclease-targeted CRISPR *trans* reporter) and SHERLOCK (specific high-sensitivity enzymatic reporter unlocking), respectively.[43,44] The Myhrvold et al.[44] assay uses Cas-13 enzyme collateral activity that nonspecifically cleaves positive strand (ss)RNA. The SHERLOCK assay uses isothermal amplification with Cas-13, an RNA-guided ribonuclease. It also uses a complimentary system (i.e., HUDSON) to reduce ribonucleases found in bodily fluids. HUDSON along with SHERLOCK helps to diagnose at point of care itself. The detection system uses a target specific known as CRISPR (cr)RNA and an ssRNA fluorescent reporter. When crRNA binds at the target site to viral nucleic acid, Cas-13 collateral

endonuclease activity cuts the RNA probe to produce a positive signal. The method was developed to detect Zika and Dengue virus.[44]

The DETECTR system developed by Chen et al. uses similar collateral endonuclease activity of enzyme Cas12a. However, the DETECTR system cleaves ssDNA rather than RNA, which is the case in SHERLOCK.[43] The investigators modified DETECTR so that it may be used to detect SARS-CoV-2. Because SARS-CoV-2 is an RNA virus, that team developed a complimentary system called RT–loop-mediated isothermal amplification (LAMP), to essentially perform RT and isothermal amplification simultaneously. Chen et al. developed targeted crRNA for Envelop protein gene (E) and Nucleo capsid gene (N) of SARS-CoV-2 for use in the DETECTR system to identify the presence of SARS-CoV-2.[43]

Both systems that are based on CRISPR/Cas are highly specific and sensitive.[43] Developed to be used at point of care, they are easy to use with lateral flow assay sticks. Such techniques can be very helpful to manage viral outbreaks because detection time is shorter, handling is easier, and results are reliable (Table 3).

D. Nucleic Acid Amplification Test

The qRT-PCR technique can be used for highly sensitive detection and analysis of viral transcriptional activity *in vivo* and *in vitro*. An accurate assessment of viral activity is critical to precisely understanding either the pathogenetic steps involved in onset and development of most viral diseases or in viral tissue tropism.[45] PCR and qRT-PCR represent the methods of choice for absolute quantitation of nucleic acids. qPCR-based procedures extend potential applications of amplification assays in molecular biology and virology. Because of its sensitivity and accuracy, qRT-PCR is commonly used as a detection method for several viral diseases in humans including hepatitis B and C viruses, human immunodeficiency virus (HIV)-1, Dengue, Ebola, SARS, and MERS.[45] Like other PCR tests, qRT-PCR uses the principle of targeted genome amplification and gives the signal in the form of fluorescence in real time.

With the outbreak of the novel SARS-CoV-2, it became imperative to develop a technique

accurate enough to diagnose and manage affected patients. Therefore, qRT-PCR is currently considered to be the gold standard for diagnosing SARS-CoV-2. The WHO recommends swab samples from the nasopharynx, oropharynx, sputum, and in some cases endotracheal aspirate from patients with symptoms associated with COVID-19. The test targets N, E, S, and RNA-dependent RNA polymerase gene ($RdRp$) gene of the virus ascertain infection; $RdRp$ has the highest analytical sensitivity.[46]

In addition to the widely used protocol of qRT-PCR to be run on N, E, and $RdRp$ of the virus, Chan et al. developed a version of qRT-PCR to diagnose SARS-CoV-2.[46] The new COVID-19–RNA-dependent RNA polymerase/helicase RdRp/Hel assay is claimed to be significantly more sensitive and specific than the available qRT-PCR technique to diagnose SARS-CoV-2 and does not cross-react with SARS.[46]

The widely used sample for detection of SARS-CoV-2 is obtained from the nasopharynx/oropharynx. But investigations performed by two different research groups suggest that a fecal sample must also be tested before a patient is released from a hospital.[47,48] These studies found that although results from nasopharynx/oropharynx samples were negative, fecal samples were positive, suggesting an oropharynx-fecal route of the virus.[47,48]

Although qRT-PCR is the standard confirmatory test for COVID-19, it has its share of shortcomings. Swab sample collection requires an expert and is not always comfortable for patients. Sample collection from lower respiratory areas can be painful. Storage and transport of samples to a dedicated lab for testing is an equally difficult task because sample handling requires utmost care. The WHO has set different parameters for storage, transport, and handling of the highly contagious samples. If the virus mutates, the technique can become inaccurate or inconclusive. Additionally, if samples are not accurately handled, the technique is liable to give false positive or false negative results. Because the technique takes nearly 4–6 hr to complete, testing a large number of people is a difficult task and can yield inconsistent results (Table 3).

E. Improved the Diagnostic Approach to Manage COVID-19

The outbreak of COVID-19 in mid-December 2020 in China placed the world on a debilitating hold and jeopardized socioeconomic activities. Countries began to screen patients with ARDS-like symptoms to rule out COVID-19 and prevent its transmission by isolating diagnosed patients. However, they failed to perform mass testing in a timely manner, and the virus spread across countries. A situation like the current pandemic demands a rapid, cheap, sensitive, specific, accurate test that can be directly used at point of care with minimal logistics and human-resource requirements. Although a specific, accurate, and sensitive method, qRT-PCR requires a great deal of expertise in collecting, handling, and running samples. PCR takes at least 4–6 hr before it yields results and its usage is greatly limited for testing a large number of individuals. Another method that can be used individually or along with qRT-PCR is a serological test for IgM/IgG antibody analysis on a card. The technique is simple and requires less time and resources than qRT-PCR. However, a negative result from an antibody test kit does not rule out the possibility of COVID-19. Moreover, positive results may suggest that infection has occurred but the result cannot be used to specify whether an individual is COVID-19 positive at the time of sample collection; the IgG antibody can remain in the blood for a long period of time, even after infection is resolved. The Standard Q COVID-19 Ag (SD Biosensor) test overcomes the limitation of antibody assays and can be used for mass screening at affordable costs; however, its sensitivity is dependent on patient viral load.[41] This pandemic requires extensive techniques to contain virus spread. To reinforce the importance of testing, we quote the WHO Director-General: "You cannot fight a fire blindfolded. And we cannot stop the pandemic if we do not know who is infected."[49]

F. Current Treatment for COVID-19 Recovery

To date, an accurate, specific, and direct treatment is not yet available for SARS-CoV-2. Currently used drugs for treatment of this disease are based on information that was previously obtained by exposure to other members of this viral group (i.e., SARS- and MERS-CoV).[15] In the current scenario, the most common treatment protocols involve quarantines (isolation of patients suspected or confirmed for COVID-19) and travel bans.[50,51] But these approaches contain limitations and if used heavily or in an unorganized manner, they will be counterproductive. COVID-19 is targeted using CT imaging, mechanical ventilation, intensive care unit admission, and indicative and sympathetic treatment approaches such as oxygen therapy (depending on the condition) and therapeutic drugs,[15,18,52] such as an antiviral drug alone or in combination with antibacterial drugs or use of monoclonal antibodies.[18] Drugs that are currently is use include remdesivir, lopinavir/ritonavir alone or in combination with interferon (IFN)-β, convalescent plasma, and monoclonal antibodies.[53]

The combination of HIV protease inhibitors lopinavir and ritonavir may have potential to treat the viral infection.[54] Of these drugs, lopinavir acts against the viral 3C-like protease and has uncertain antiviral activity against SARS-CoV-2. The combination of lopinavir with ritonavir (to enhance bioavailability) and immunomodulator IFN-β1b is in clinical trials (ClinicalTrials.gov; NCT02845843) to treat MERS. This combination, extensively available on a large scale, is used in various case reports and case series against SARS-CoV-2.[54]

In a clinical trial of lopinavir–ritonavir for SARS-CoV-2 infection no substantial progress was found.[55] Drug efficacy was evaluated orally in a randomized, organized, open-label trial named Lopinavir Trial for Suppression of SARS-CoV-2 in China in COVID-19 adult patients and completed with benefits below the standard of care.[55]

G. Artificial Intelligence and COVID-19

In the race to develop a robust system to test, diagnose, and curb the spread of COVID-19, we can use artificial intelligence (AI) models to make real-time decisions. AI models can reduce the time taken to manually identify a Covid-positive test, an X-ray scan, or CT scan. AI-driven models that are

trained cross-population can be used in cross-countries.[56] Cross-population trained tools mean that an AI model is fed data from one country and the data is used in a different country, creating a robust and agile system.[56] AI can accelerate the number of COVID-19 scans (X-ray, CT, or magnetic resonance imaging) in 1 d. Data from cities, states, and villages can be fed to AI-driven models to detect rate of infection, location of clusters, and whether ongoing quarantine measures are working. And the quest does not stop there. Mukherjee et al. successfully engineered a convolutional neural network–tailored deep neural network. This structure was used to train AI models to detect COVID-19 via CT scans.[57] Mukherjee et al. reported 96% accuracy with this model of detection. This may accelerate development of AI models for detection of COVID-19 on a large scale.[57] Such measures can help to make robust decisions in real time to stop infection.[58]

H. Therapeutic Possibilities for Preventing COVID-19

Many research groups are working feverishly to develop a safe and effective vaccine for COVID-19 by exploiting the high level of genetic similarity between SARS-CoV and SARS-CoV-2, assuming that successful vaccines against SARS-CoV may also be effective against SARS-CoV-2. Researchers target the glycoprotein spike (S) on the surface or S protein via S-protein and S-cleavage inhibitors, receptor binding domain (RBD)-ACE2 blockers, small interfering (si)RNAs, fusion core blockers, protease inhibitors, and antibodies for neutralization. Attempts have been made to develop S-protein–based CoV vaccines by exploring the complete S protein or S1 RBD and expression in virus-like particles, DNA, or viral vectors.[59–63] Moreover, RNA synthesis inhibitors (tenofovir disoproxil fumarate and lamivudine), remdesivir, neuraminidase inhibitors, peptide (EK1), anti-inflammatory drugs, abidol, and Chinese traditional medicine (e.g., Lianhuaqingwen and ShuFengJieDu) serve as potential therapeutics for COVID-19. Despite successful attempts at anti-CoV actions via *in vitro* studies (mostly), these agents cannot be used to treat COVID-19 due to lack of adequate animal and clinical studies.[64]

By exploiting information related to the biology of SARS-CoV-2, agents such as cepharanthine (CEP), selamectin, and mefloquine hydrochloride can be effective against COVID-19. CEP is highly suggested to be a wide-range inhibitor of pan-*Betacoronavirus* and is believed clinical trials will prove it beneficial for COVID-19 patients.[65]

Epitopes for COVID-19 vaccine candidates can be recognized using the immunoinformatics method, which found substantial cytotoxic T-lymphocyte (CTL) and B-cell epitopes in the SARS-CoV-2 S protein. In addition, molecular-dynamics simulations found interactions among these epitopes and their equivalent major histocompatibility complex (MHC) class I molecules, confirming binding of CTL epitopes with MHC class I peptide-binding channels through several interactions and potential to produce an immune response.[66] Thus, these epitopes can be exploited to develop an effective COVID-19 vaccine.

Exonuclease properties of nonstructural protein 14 can be deactivated or the envelope protein in SARS can be deactivated via reverse genetic approaches to develop live-attenuated vaccines. The avian live infectious bronchitis virus (IBV) vaccine (strain H) was developed to neutralize avian IBV, a chicken CoV that may have potential to serve as a beneficial tool to neutralize SARS. H strain neutralizes the construction of antibody along with additional immune responses.[59] After ensuring vaccine safety, it can be beneficial in stopping transmission of COVID-19 infection.

Monoclonal antibodies (mAbs) can serve as active tools to regulate CoV because they may directly interfere in exposed individuals, as found in recovered patients. RBD-specific mAbs prominently depend on resemblance among their RBDs to cross-neutralize SARS-CoV. This is the main reason that RBD-specific SARS-CoV antibodies may cross-neutralize SARS-like (SL) CoVs, such as bat-SL-CoV strain WIV1 RBD, which has eight amino acid alterations compared to SARS-CoV but is not effective against bat-SL-CoV strain SHC014 (with 24 amino acid variances). Therefore, these RBD-specific mAbs have potential to be assessed further for neutralizing SARS-CoV-2. In addition, combination a therapy of mAbs plus remdesivir

may emerge as the model therapeutic prospect for COVID-19.[67]

Other therapeutic alternatives could be assessed for effectiveness against COVID-19. These alternatives include identifying or screening molecules/neutralizing antibodies/mAbs that can bind to specific virus receptors, interfere with S1 RBD, antiviral peptide targeting S2 or inhibitors/siRNA, antisense RNA and ribozyme to target particular proteins/enzyme of virus replication/translation, inhibitors to target helicase/proteases, additional virus proteins, and host cell endocytosis.[61,68] In addition, a number of anti-CoV compounds are available, but most are in the preclinical stage and require further assessment. Some of these compounds/agents are in clinical trials (phase III) for COVID-19, such as remdesivir, oseltamivir, ASC09F (HIV protease inhibitor), lopinavir, ritonavir, darunavir, and cobicistat.[69]

V. CONCLUSIONS AND FUTURE PROSPECTIVES

Improved diagnosis and treatment are crucial to overcome the threat of this pandemic. Researchers/experts around the world suggest development of a more specific serological test to rule out the possibility of COVID-19 and can be used for mass testing. The use of technologies developed using CRISPR such as SHERLOCK and DETECTR can be candidates for COVID-19 diagnosis as well. Because tests developed with the use of CRISPR-Cas are accurate and specific, their mass production will certainly help in widespread testing at point of care itself, with minimal expertise and logistics requirement. Because sample collection in the case of qRT-PCR can be uncomfortable and CRISPR-Cas just needs a drop of blood to run, this makes it more patient friendly. CRISPR-Cas might just be the ideal candidate for SARS-CoV-2 diagnosis, but it must be cost effective or the whole point of mass testing will be defeated. SARS-CoV-2 infection initiated severe societal damage with adverse effects on the public's lives and economies globally. It is a matter of critical concern to develop prompt detection/diagnostic approaches and appropriate treatments to prevent, control, and neutralize this pandemic virus urgently.

REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard [database on the Internet]. Geneva, Switzerland: World Health Organization; c2020 [cited 2021 Jan 7]. Available from: https://covid19.who.int/.

2. Vassilara F, Spyridaki A, Pothitos G, Deliveliotou A, Papadopoulos A. A rare case of human coronavirus 229E associated with acute respiratory distress syndrome in a healthy adult. Case Rep Infect Dis. 2018 Apr 15;2018:6796839.

3. Kaiser L, Regamey N, Roiha H, Deffernez C, Frey U. Human coronavirus NL63 associated with lower respiratory tract symptoms in early life. Ped Infect Dis J. 2005 Nov 1;24(11):1015–7.

4. Zhang SF, Tuo JL, Huang XB, Zhu X, Zhang DM, Zhou K, Yuan L, Luo HJ, Zheng BJ, Yuen KY, Li MF. Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010–2015 in Guangzhou. PLoS One. 2018 Jan 29;13(1):e0191789.

5. Friedman N, Alter H, Hindiyeh M, Mendelson E, Shemer Avni Y, Mandelboim M. Human coronavirus infections in Israel: Epidemiology, clinical symptoms and summer seasonality of HCoV-HKU1. Viruses. 2018 Oct;10(10):515.

6. Human Coronavirus Types [database on the Internet]. Atlanta, GA: Centers for Disease Control and Prevention. c2020 - [updated 2020 Feb 15; cited 2021 Jan xx]. Available from: https://www.cdc.gov/coronavirus/types.html.

7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020 May 1;109:102433.

8. Dowd JB, Andriano L, Brazel DM, Rotondi V, Block P, Ding X, Liu Y, Mills MC. Demographic science aids in understanding the spread and fatality rates of COVID-19. Proc Natl Acad Sci. 2020 May 5;117(18):9696–8.

9. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020 May 26;323(20):2052–9.

10. Guan WJ, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, Liu X-Q, Chen R-C, Tang C-L, Wang T, Ou C-Q, Li L, Chen P-Y, Sang L, Wang W, Li J-F, Li C-C, Ou L-M, Cheng B, Xiong S, Ni Z-Y, Xiang J, Hu Y, Liu L, Shang H, Lei C-L, Peng Y-X, Wei L, Yong L, Hu Y-H, Peng P, Wang J-M, Lui J-Y, Chen Z, Li G, Zheng Z-J, Qiu S-Q, Luo J, Ye C-J, Zhu S-Y, Cheng L-L, Ye F, Li S-Y, Zheng J-P, Zhang N-F, Zhong N-S, He J-X, China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J. 2020 May 1;55(5):2000547.

11. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu

Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Yuan L, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New Engl J Med. 2020;382:1199–207.

12. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020 May 1;55(5):105955.

13. Broughton JP, Deng X, Yu G, Fasching CL, Servellita V, Singh J, Miao X, Streithorst JA, Granados A, Sotomayor-Gonzalez A, Zorn K. CRISPR–Cas12-based detection of SARS-CoV-2. Nat Biotechnol. 2020 Jul;38(7):870–4.

14. Freeman B, Lester S, Mills L, Rasheed MAU, Moye S, Abiona O, Hutchinson GB, Morales-Betoulle M, Krapinunaya I, Gibbons A, Chiang C-F, Cannon D, Klena J, Johnson JA, Owen SM, Graham BS, Corbett KS, Thornburg NJ. Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and serosurveillance. bioRxiv. 2020 Apr 25. doi: 10.1101/2020.04.24.057323.

15. Dhama K, Sharun K, Tiwari R, Dadar M, Malik YS, Singh KP, Chaicumpa W. COVID-19, an emerging coronavirus infection: Advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccines Immunother. 2020 Jun 2;16(6):1232–8.

16. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island, FL: StatPearls Publ; 2021.

17. Chan JF-W, Kok K-H, Zhu Z, Chu H, To KK-W, Yuan S, Yuen K-Y. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020 Jan 28;9(1):221–36.

18. Li Y, Guo F, Cao Y, Li L, Guo Y. Insight into COVID-2019 for pediatricians. Ped Pulmonol. 2020 May;55(5):E1–4.

19. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L, Shang Y. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: Experts' consensus statement. World J Ped. 2020 Jun;16(3):223–31.

20. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. Curr ProbL Cardiol. 2020 Aug; 45(8):100618.

21. Kuhn JH, Li W, Choe H, Farzan M. Angiotensin-converting enzyme 2: A functional receptor for SARS coronavirus. Cell Mol Life Sci. 2004 Nov 1;61(21):2738–43.

22. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C-L, Chen H-D, Chen J, Luo Y, Guo H, Jiang R-D, Liu M-Q, Chen Y, Shen X-R, Wang X, Zhen X-S, Zhao K, Chen Q-J, Deng F, Liu L-L, Yan B, Zhan F-X, Wang Y-Y, Xiao G-F, Shi Z-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–3.

23. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271–80.

24. Salzberger B, Glück T, Ehrenstein B. Successful containment of COVID-19: The WHO-report on the COVID-19 outbreak in China. Infection. 2020 Apr;48(2):151–3.

25. Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, Zheng C. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: A preliminary analysis. Am J Roentgenol. 2020 Jul;215(1):127–32.

26. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, Hamie QM, Meier CF, Hunziker S, Forras-Kaufmann Z, Kuyumcu S. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids. 2015 Apr 1;47(4):693–705.

27. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020 Aug;81(5):537–40.

28. Fischer S-C, Kohler K, Wenger A. Digital technologies in corona crisis management. Zurich, Switzerland: Center for Security Studies ETH Zurich; 2020.

29. Li J, Guo X. COVID-19 contact-tracing apps: A survey on the global deployment and challenges. Cornell University arXiv preprint arXiv:2005.03599 [cs.CR]. Comp Sci Cryptog Secur. 13 May 2020.

30. Tay MR, Low YL, Zhao X, Cook AR, Lee VJ. Comparison of infrared thermal detection systems for mass fever screening in a tropical healthcare setting. Publ Health. 2015 Nov 1;129(11):1471–8.

31. Li Y, Xia L. Coronavirus disease 2019 (COVID-19): Role of chest CT in diagnosis and management. Am J Roentgenol. 2020 Jun;214(6):1280–6.

32. To KK-W, Hung IF-N, Ip JD, Chu AW-H, Chan W-M, Tam AR, Fong CH-Y, Yuan S, Tsoi H-W, Ng AC-K, Lee LL-Y, Wan P, Tso E, To W-K, Tsang D, Chan K-H, Huang J-D, Kok K-H, Cheng VC-C, Yuen K-Y. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020 Aug 25;ciaa1275. doi: 10.1093/cid/ciaa1275.

33. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia. Mil Med Res. 2020 Dec;7(1):1–23.

34. Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, Zeng B, Li Z, Li X, Li H. Diagnosis of the coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020 May 1;126:108961.

35. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, Guo F, Zhao H, Gao R. A comparative study on the clinical

features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis. 2020 Mar 12. doi: 10.1093/cid/ciaa247.

36. Zhao D, Zheng FY, Guo YG, Gao HZ. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias; Clinical Infectious Diseases; Oxford Academic. Clinical Infectious Diseases.

37. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, Sun R, Wang Y, Hu B, Chen W, Zhang Y. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020 Sep;92(9):1518–24.

38. Capello F, Cipolla M, Cosco L, Gnasso A, Mancini R, Nichelatti M, Savo MT, Gaddi AV. The VivaDiag COVID-19 IgM/IgG rapid test for the screening and early diagnosis of COVID-19 in patients with no clinical signs of the disease. Int J Endocrinol Metab Disord. 2020;6(1). doi.org/10.16966/2380-548X.167.

39. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis. 2020 Jul 28;71(15):778–85.

40. jmitra.co.in [homepage on the Internet]. New Delhi, India: J. Mitra & Co. Pvt. Ltd., c2020. COVID 19 (IGM + IGG + IGA) MICROLISA [cited 2020 Jul xx]. Available from: http://jmitra.co.in/services_details.aspx?id=73&name=-COVID%2019%20(IgM%20+%20IgG%20+%20IgA)%20MICROLISA.

41. SD Biosensor [homepage on the Internet]. Gyeonggi-do, Korea: SD Biosensor. c2020. STANDARD Q COVID-19 Ag [cited in 2020 Jul xx]. Available from: http://sdbiosensor.com/xe/product/7672.

42. Makarova KS, Haft DH, Barrangou R, Brouns SJ, Charpentier E, Horvath P, Moineau S, Mojica FJ, Wolf YI, Yakunin AF, Van Der Oost J. Evolution and classification of the CRISPR–Cas systems. Nat Rev Microbiol. 2011 Jun;9(6):467–77.

43. Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, Doudna JA. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science. 2018 Apr 27;360(6387):436–9.

44. Myhrvold C, Freije CA, Gootenberg JS, Abudayyeh OO, Metsky HC, Durbin AF, Kellner MJ, Tan AL, Paul LM, Parham LA, Garcia KF. Field-deployable viral diagnostics using CRISPR-Cas13. Science. 2018 Apr 27;360(6387):444–8.

45. Clementi M, Menzo S, Bagnarelli P, Manzin A, Valenza A, Varaldo PE. Quantitative PCR and RT-PCR in virology. PCR Meth Appl. 1993 Feb 1;2:191.

46. Chan JF-W, Yip CC-Y, To KK-W, Tang TH-C, Wong SC-Y, Leung K-H, Fung AY-F, Ng AC-K, Zou Z, Tsoi HW, Tsoi H-W, Choi GK-Y, Tam AR, Cheng VC-C, Chan K-H, Tsang OT-Y, Yuen K-Y. Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/Hel real-time reverse transcription-PCR assay validated in vitro and with clinical specimens. J Clin Microbiol. 2020 Apr 23;58(5):e00310–20.

47. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, Yang Y, Liu B, Wang W, Wei C, Yang J. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020 Jul;92(7):833–40.

48. Chen C, Gao G, Xu Y, Pu L, Wang Q, Wang L, Wang W, Song Y, Chen M, Wang L, Yu F. SARS-CoV-2–positive sputum and feces after conversion of pharyngeal samples in patients with COVID-19. Ann Intern Med. 2020 Jun 16;172(12):832–4.

49. Salathé M, Althaus CL, Neher R, Stringhini S, Hodcroft E, Fellay J, Zwahlen M, Senti G, Battegay M, Wilder-Smith A, Eckerle I, Egger M, Low N. COVID-19 Epidemic in Switzerland: On the importance of testing, contact tracing and isolation. Swiss Med Wkly. 2020 Mar 19;150:w20225.

50. Parmet WE, Sinha MS. COVID-19—the law and limits of quarantine. New Engl J Med. 2020 Apr 9;382(15):e28.

51. Ahmad T, Khan M, Khan FM, Hui J. Are we ready for the new fatal Coronavirus? Scenario of Pakistan. Hum Vaccines Immunother. 2020 Mar 3;16(3):736–8.

52. Nakajima K, Kato H, Yamashiro T, Izumi T, Takeuchi I, Nakajima H, Utsunomiya D. COVID-19 Pneumonia: Infection control protocol inside computed tomography suites. Jpn J Radiol. 2020 May:398(5):391–3.

53. Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 novel Coronavirus. Zhonghua Jie He He Hu Xi Za Zhi. Chinese J Tuberc Respir Dis. 2020 Feb 5;43(0):E002.

54. Baden LR, Rubin EJ. COVID-19—the search for effective therapy. New Engl J Med. 2020;382:1851–2.

55. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan C, CHen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Chen F, Pan L, Zou J, Jua C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Hornby PW, Zhang D, Wang C. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. New Engl J Med. 2020;382:1787–99.

56. Santosh KC. AI-driven tools for coronavirus outbreak: Need of active learning and cross-population train/test models on multitudinal/multimodal data. J Med Syst. 2020 May;44(5):1–5.

57. Mukherjee H, Ghosh S, Dhar A, Obaidullah SM, Santosh KC. Deep neural network to detect COVID-19: One architecture for both CT scans and chest X-rays. Appl Intell. 2020. doi.org/10.1007/s10489-020-01943-6.

58. Jamshidi M, Lalbakhsh A, Talla J, Peroutka Z, Hadjilooei F, Lalbakhsh P, Jamshidi M, La Spada L, Mirmozafari M, Dehghani M, Sabet A. Artificial intelligence and

COVID-19: Deep learning approaches for diagnosis and treatment. IEEE Access. 2020 Jun 12;8:109581–95.

59. Graham RL, Donaldson EF, Baric RS. A decade after SARS: Strategies for controlling emerging coronaviruses. Nat Rev Microbiol. 2013 Dec;11(12):836–48.

60. Jiang S, He Y, Liu S. SARS Vaccine development. Emerg Infect Dis. 2005 Jul;11(7):1016.

61. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226–36.

62. Ji W, Wang W, Zhao X, Zai J, Li X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. J Med Virol. 2020;92(4). doi: 10.1002/jmv.25682.

63. Widjaja I, Wang C, van Haperen R, Gutiérrez-Álvarez J, van Dieren B, Okba NM, Raj VS, Li W, Fernandez-Delgado R, Grosveld F, van Kuppeveld FJ. Towards a solution to MERS: Protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. Emerg Microbes Infect. 2019 Jan 1;8(1):516–30.

64. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020 Feb 29; 14(1):69–71.

65. Fan H-H, Wang L-Q, Liu W-L, An X-P, Liu Z-D, He X-Q, Song L-H, Tong Y-G. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Chin Med J. 2020 May 5;133(9):1051–6.

66. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. J Med Virol. 2020 May;92(5):495–500.

67. Cohen J. New coronavirus threat galvanizes scientists. Science. 2020 Jan 31;367(6477): 492–3.

68. Kumar V, Jung Y-S, Liang P-H. Anti-SARS coronavirus agents: A patent review (2008–present). Expert Opin Ther Pat. 2013 Oct 1;23(10):1337–48.

69. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Rev Drug Disc. 2020 Mar;19(3):149–50.