REVIEW ARTICLE

Recent Development in Diagnosis and Treatment of COVID-19 Pandemic

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ABSTRACT

Coronavirus disease (COVID-19) is a transmissible disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The primary clinical expression of COVID-19 is an acute respiratory illness with interstitial and alveolar pneumonia. The virus originated in late 2019 in Wuhan, Hubei Province, China. The infectious agent, based upon genetic studies is of zoonotic origin and spread in the local population possibly through community spread by persons shopping at wet animal market, where live wild game is sold. The rapid spread of COVID-19 led it to be declared a global pandemic by the WHO. As of September 21, 2020, 30,675,675 cumulative cases of COVID-19 have been reported worldwide with 954,417 cumulative deaths. The diagnosis of COVID-19 is based primarily on epidemiological factors, clinical symptoms, and laboratory testing techniques such as hemography, chest computed tomography, and virology examination. To date, there are no clinically approved vaccines or antiviral drugs available for use against COVID-19. Nevertheless, in clinical trials, a few broad-spectrum antiviral drugs as well as repurposed drugs approved for other indications have been assessed against COVID-19. In this review, we highlight the epidemiology, symptoms, transmission, pathogenesis of the COVID-19, with emphasis on current progress in rapid diagnosis and treatment options.

Key Words: *COVID-19, Diagnosis, Drugs, Global Cases and Deaths, Vaccine.*

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is spreading around the world, causing distress and fear in humans from all sectors of life.[1] The virus was publicly reported in late December 2019 from Wuhan, Hubei Province, China.[2] The affected patients suffered from pneumonia and were linked to their proximity to a seafood and wet animal wholesale market in Wuhan city. Initially, seven confirmed cases of pneumonia whose clinical features matched those of viral pneumonia were reported during 8-18 Dec 2019. As secondary and tertiary cases emerged, China's office of the World Health Organization (WHO) reported the incidence of these cases and their etiological pneumonia on 31 Dec 2019. Further, additional 44 patients were reported to WHO having similar symptoms during the period of 31 Dec 2019 to 3 Jan 2020.

Chinese researchers identified the epidemic etiologic agent as a previously unknown coronavirus on 7 Jan 2020[3] The virus isolated from these patients was named novel coronavirus 2019 (2019-nCoV).[1] The virus soon moved from Hubei Province into other regions of China and to other nearby countries, including South Korea, Thailand, and Japan. Driving disease spread was widespread travel of infected people, many with mild symptoms or with no symptoms, to above-mentioned countries.[3,4] The WHO declared the outbreak as a public health emergency of international concern on 30 Jan 2020.

On 11 Feb, 2020, the disease was named "coronavirus disease 2019" (COVID-19) by WHO.[5,6]

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One month later, on March 11, 2020, WHO declared the outbreak of COVID-19 a global pandemic.[7] According to WHO COVID-19, as of September 21, 2020, 30,675,675 cumulative cases of COVID-19 have been reported globally with 954,417 cumulative deaths (Fig 1).[8]

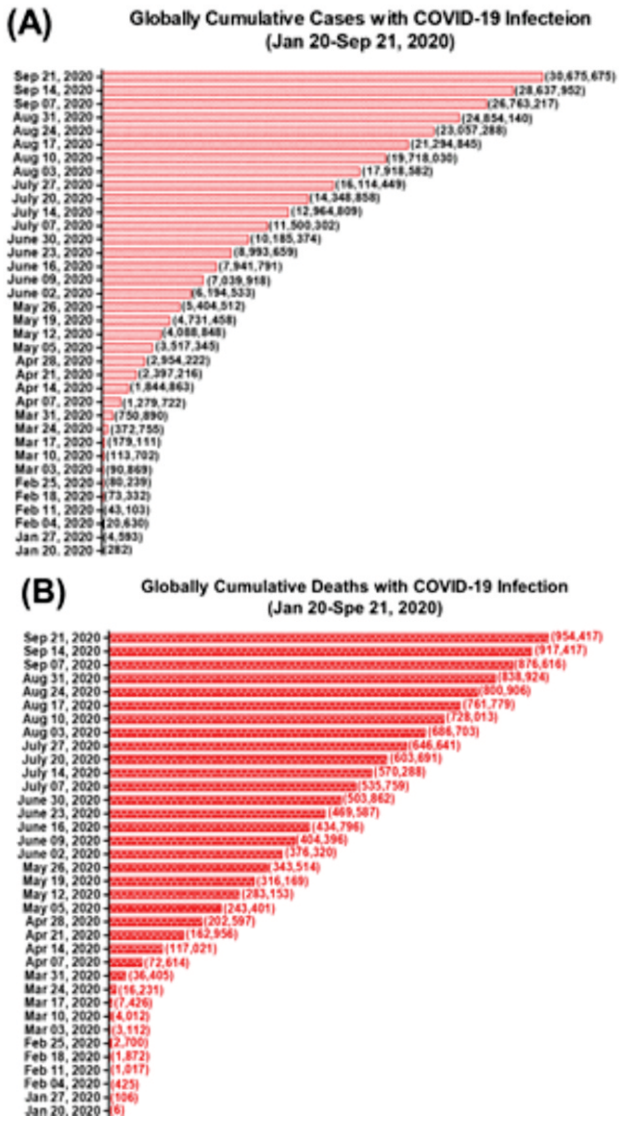

Fig 1: Globally Incidence of COVID-19 in between Jan 20 to September 21, 2020. Globally cases (A) and deaths (B) with COVID-19 in chronological order

The number of confirmed COVID-19 cases in the most severely affected countries is sure to rise for at least many months, absent new effective treatment options, especially in the United States and Europe. As of September 21, 2020, 15,466,584 (50%) cases and 527, 837 (55%) deaths have been reported in the regions of the Americas (Fig 2).

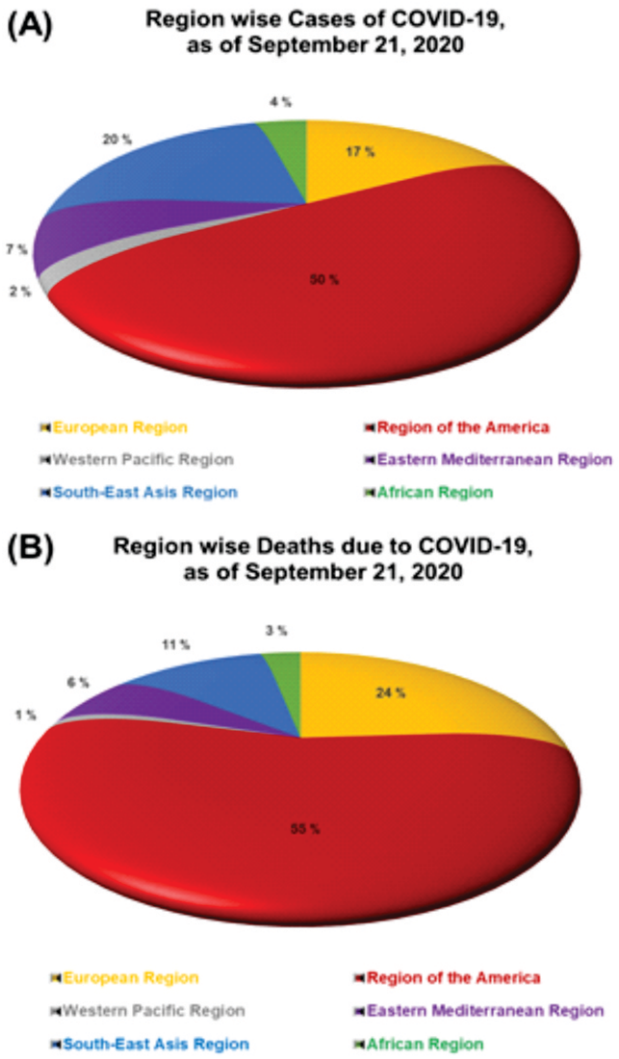

Fig 2: As of 21 September 2020, globally region-wise distribution of COVID-19 cases (A) and deaths (B) indicates that Americas and European regions have the highest incidence

The highest number of COVID-19 cases and deaths is reported from the United States which is 6,662,003 and 197,442, respectively.[8] As of September 21, 2020, 5,195,853 (17%) cases and 229,802 (24%) deaths have been reported in the European region.[8] Currently, there is no effective vaccines or drug for COVID-19 therapy. The COVID-19 pandemic poses significant political, economic, scientific, public health and health care facilities challenges.[9]

2. A brief history of coronaviruses and human diseases

Coronaviruses are enveloped RNA viruses that are widely distributed among humans, other mammals, and birds causing respiratory, enteric, hepatic, and neurological diseases.[10] Coronaviruses were first

identified by Tyrell and Bynoe in 1966, who cultured the viruses from common cold patients.[11] In Latin, corona means crown. The coronavirus family got their name because of their common visual appearance, having spike-like projections from the outer membrane that resemble a crown.[12] Prior to the current outbreak there were six named coronaviruses: 229E, OC43, NL63, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV).[13] The first four viruses typically cause common cold symptoms in those with immunocompetence. However, SARS-CoV and MERS-CoV often associated with severe lower respiratory tract infections.[14]

SARS-CoV was the causative agent for the 2002 and 2003 drastic outbreaks of acute respiratory syndrome in Guangdong Province, China.[15] MERS-CoV was the pathogen responsible for the Middle East outbreaks of severe respiratory disease in 2012.[16] The SARS-CoV epidemic was spread to 37 countries and was associated with 8096 infected cases and 774 deaths. MERS-CoV was spread to 27 countries, causing 2494 infected cases and 858 deaths worldwide.[17]

As of December 2019, SARS-CoV-2 (also known as 2019-nCov) was added as a seventh member of the family of coronaviruses known to infect humans and capable of human to human transmission. Historically, bats are known as natural reservoirs of many highly pathogenic viruses, including SARS-CoV and MERS-CoV.[17,18] Therefore, several studies proposed that bat-to-human zoonotic transmission, either directly or through an intermediate wild animal host, gave rise to SARS-CoV2.[19,20] Several reports, including WHO studies, describe early evidence for human-to-human transmission and the rapid intercity and global spread of SARS-CoV2.[3,21,22]

3. Symptoms of COVID-19

Symptoms of COVID-19 can vary widely, but severe cases tend to involve a sudden, highly lethal pneumonia with similar clinical symptoms as reported for SARS-CoV and MERS-CoV infections. The most common symptom of COVID-19 patients is respiratory failure, and most patients admitted to the intensive care were unable to breathe spontaneously and have low blood oxygen levels by pulse oximetry. Symptoms of upper respiratory infection with rhinorrhoea and productive cough are uncommon, except in children.[23] Fever and respiratory symptoms usually occur in COVID-19 patients, and some patients also experience gastrointestinal symptoms such as diarrhea and abdominal pain.[24,25] In addition, some COVID-19 patients have displayed neurological symptoms such as headache, fatigue, and vomiting.[26] A general decline in taste and odor perceptions has been commonly noted.

COVID-19 infection appears to be initiated by binding a viral spike protein to ACE2, which is widely expressed in the lung. ACE2 has a wide pattern of expression in human cell types, being highly expressed in the gastrointestinal system, heart, and kidney, with more recent evidence recognizing ACE2 expression in alveolar cells of type II in the lungs.[27] Binding prompts internalization of the virus, which primarily invades the alveolar epithelial cells. The body immune system responds by releasing cytokines and other inflammatory mediators which resulting in symptoms of pneumonia. The pathological features of COVID-19, SARS-CoV and MERS-CoV greatly resemble.

4. Diagnosis

Accurate diagnosis of COVID-19 is still a challenging task for medical practitioners and diagnostic scientists around the globe. The following section elaborates the most common diagnostic methods for COVID-19.

Clinical diagnosis

Clinical symptoms of the COVID-19 infections vary from person to person, however, most of the common clinical symptoms, noted above, include fever, fatigue, dry cough, dyspnoea etc., which can be (though often are not) accompanied by runny nose, nasal congestion or other upper respiratory symptoms.[28] Because fevers can be readily assessed, even without contact with a patient, detection of elevated body temperature has been a front-line screen for possible COVID-19 infection, though naturally many other diseases are also marked by fevers, and patients with latent but transmissible SARS-CoV2 infection can have normal body temperatures. Various other methods for clinical diagnosis are discussed below.

Patient physical examination

Physical examination, beyond fever assessment, is

useful in COVID-19 diagnosis. However, the issue of asymptomatic carriers is again confounding: patients with mild symptoms or no symptoms may not present with directly observable evidence for infection. In contrast, patients with disease in a non-latent stage often show clear symptoms such as moist rales in lungs, shortness of breath, weakened breath sounds, tactile speech tremor and dullness in percussion, and such signs prompt further investigations to confirm the infection.

Computed tomography scan

A computed tomography scan (CT scan) offers more detailed information as compared with X-ray analysis. A CT scan combines multiple images taken from various angles around the body, processed using a computer, and giving the clinician cross-sectional 3D images (slices) of the body part scanned. CT scans in the early stages of COVID-19 associated pneumonia show multiple small patchy shadows and interstitial changes[29], remarkable in the lung periphery.[30] However, bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary consolidation is observed in more severe cases. In comparison to X-rays, CT scans show more detail for pulmonary lesions, such as ground-glass opacity and segmental consolidation in bilateral lungs, especially in the lung periphery. These findings are similar to those reported with SARS[31,32] and MERS[33,34], and is perhaps characteristic of pneumonia caused by coronaviruses.

Laboratory diagnosis

Ultra-sensitivity, specificity, and rapid assessment are the main objectives for laboratory-based tests and have been a challenging task in the current COVID-19 pandemic. Virus isolation and viral nucleic acid detection are considered to be the gold standard for COVID-19 diagnosis. The test is performed using various specimens such as nasopharynx or trachea extracts, nasal swabs, sputum or lung tissue, faeces and blood.[35] This technique is used as an early diagnostic tool for COVID-19 nucleic acid. While SARS-CoV-2 is known to undergo mutations in structure, its modest rate of genetic drift is currently not expected to thwart its accurate and precise detection.

Reference test

The most accurate diagnosis of COVID-19 at the laboratory level is a real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) assay[36] which is also called a reference test. Concisely, the assay performed as follows: at first, swaps are collected either nasopharyngeal (NP) and/or oropharyngeal (OP), then rRT-PCR assay utilizes viral RNA extracted from patient samples, the complementary DNA (cDNA) synthesized by the action of the reverse transcriptase enzyme. This process amplifies target sequences of the viral genome from the cDNA template. The obtained information is typically interpreted in a semi-quantitative manner. Most importantly, target amplification speed is dependent on the quality and quantity (concentration) of viral RNA in the initial sample, where the amplification speed can be considered as a proxy for sample load of the virus. However, a negative result is interpreted when the amplification process fails. It is worth mentioning that in some cases false-negative results can be obtained due to the poor quality of the clinical sample (for example, live virus may have been initially present, but became non-viable before analysis) or because of a very low viral titer, characteristic of early disease status.

Serological, antigen, and antibody testing

The serological tests are based on enzyme-linked immunosorbent assays (ELISA). The method detects either presence or absence of the COVID-19 antibodies in human samples such as blood, plasma or serum.[37] The assay detects immunoglobulins M and G (IgM and IgG), where the former is the first and largest to appear after exposure to an antigen. In contrast, IgG will appear at later stages. The aim of this type of testing is that to determine if the patient has previously been infected with COVID-19, the test stays positive after active infection has gone. Unfortunately, many of the serological tests, though they have been used to address testing shortfalls, can be considered under development and not yet fully validated for rates of false positives or false negatives. This has eroded confidence in the interpretation of early antibody studies. Similarly, an antigen test[38] can provide supplementary data either during or before molecular screening. However, there is no readily available marketed (commercially) antigen tests for COVID-19 during the time of this manuscript writing.

Though testing for antibodies is well established, some serious challenges remain. As mentioned

above, accuracy and specificity must be quantified for results to be useful. Not all antibodies that are detectable are necessarily disease-modifying antibodies, so the degree of protection from further infection is yet unclear. Further, antibody testing methods typically require more time to have elapsed post disease onset to get a meaningful result. The test itself can be lengthy, requiring viral components to be produced and requiring additional steps such as purification and standardisation. In contrast, the rRT-PCR is considered as gold standard for COVID-19 testing because of its accuracy, sensitivity, and relative simplicity. However, the high instrumentation and technician labour requirements of rRT-PCR testing can overburden centralized laboratories, slowing diagnosis and raising testing expenses.

Point of care (POC) devices

Many point of care devices are still in developing stages, with some showing hints of success, though not yet gaining approval of regulatory agencies.[39] At least 6 POC devices have been developed so far that are summarized in Table 1. Typically, swab samples are required to perform the test except for MicrosensDx, which also supports sputum samples. There are few differences in the operation, number of samples, sample preparation time, and processing time.

Table 1: Molecular point-of-care diagnostic assays

Product	Type of sample	FDA Approved	Result time	Target	Method
Accula SARS-CoV-2 (Mesa Biotech)	Throat and nasal swabs	Yes	30 mint	SARS-CoV-2 RNA	RT-PCR + lateral flow
VitaPCR COVID-19 assay (Credo)	NP or OP swabs	Yes	20 mint	SARS-CoV-2	RT-PCR
ePlex SARS-CoV-2 (GenMark Diagnostics)	NP swab	Yes	<2 mint	SARS-CoV-2 RNA	RT-PCR
RapiPrep COVID-19 (Microsens Dx)	Sputum swabs	Awaiting	8-10 min	SARS-CoV-2	LAMP amplification
Xpert SARS-CoV-2 (Cepheid)	NP swab, nasal aspirate	Yes	45-60 min	SARS-CoV-2 RNA	RT-PCR
ID NOW COVID- 19 (Abbott Diagnostics)	Throat, nasal, NP and OP swabs	Yes	13 min	SARS-CoV-2 nucleic acid	Isothermal nucleic acid amplification

Antibody POC diagnostics

As stated above, the antibody-based assay is based on the detection of IgG and IgM in various human samples. To date, at least 5 such antibody POC devices are reported and they operate by different mechanisms. BioMedomics and Surescreen are based on lateral flow immunoassays. VivaDiag COVID-19 IgG-IgM and Assay Genie rapid POC kit tests are based on colloidal gold immunoassays. The Goldsite diagnostics kit utilises time-resolved fluorescence immunoassay. The results are depicted as lines similar to pregnancy test results, within 10-15 minutes. Single-use disposable cartridges are used and most of them can be kept at RT (room temperature). BioMedomics[40], displayed 89, 91% sensitivity and specificity, respectively.

Overall, there is much interest in this area of diagnostic research, driven by the potential for quick and clear results not requiring laboratory analysis, though the gold standard for COVID-19 diagnosis remains rRT-PCR. Normally, diagnostic evaluation are expected to be lower in clinical atmosphere on contrary to well controlled laboratory environment. The development of accurate and scalable POC tests for the diagnosis of COVID-19, is expected to continue and may offer advantages in rapid and widespread diagnosis.[41,42] Fabrication of such devices will not only reduce detection time but will also enhance proper use of measures to control infection, isolation resources, and recruitment into clinical trials. Types of diagnostic approaches for COVID-19 are summarized in Table 2.

Table 2: Summary of diagnostic tests for COVID -19

Diagnostic test	Detection mechanism	Testing sample	Interpretation if positive	Detectable period	Status of use
Clinical tests	Clinical symptoms (Fever/cough) etc	CT scan	Possibly infected	From few days after onset of symptoms	All countries
Antibody based immunoassay	ELISA detection of IgM, IgG	Serum	IgM+: 3-5 days post onset IgG past infection	From 7-28 days after onset of symptoms	Some regions
Antigen based immunoassay	ELISA detection of viral protein e.g. S (spike) or N (nucleocapsid	NP swap, serum, feces	Confirm SAR-CoV-2 infection	From few days after onset of symptoms	Some regions
Nucleic acid amplification	rRT-PCR, detection of genetic sequence	NP, OP swaps, sputum in hospital, feces	Confirm SAR-CoV-2 infection	All stages	All countries

5. COVID-19 treatment updates

As the outbreak of COVID-19 turned into a pandemic and total cases worldwide exceeded 3 million, health authorities, scientists, and the pharmaceutical industry have begun to find potential treatments to alleviate disease conditions and to prevent further spread of the virus. Various possible treatment strategies are being considered by researchers and scientists worldwide. These include drug repurposing strategies, new drug discovery efforts, vaccination, convalescent plasma, and other miscellaneous therapies. In this section, we describe the current development in ongoing treatment strategies for the COVID19 pandemic, with areas summarized in Table 3.

QMC (Queen's Medical Centre), SGIMI (Shenzhen

Table 3: Emerging treatment options for COVID-19

Treatment strategies	Candidates	Characteristics	Lead developers	Clinical trials
Drugs	Hydroxychloroquine	Antimalarial	QMC	Phase III (NCT04345692)
	Remdesivir	A nucleotide analogue viral RNA polymerases inhibitor	Gilead Ph.	Phase III (NCT04292899)
	Actemra (tocilizumab)	A monoclonal antibody approved by FDA for rheumatoid arthritis	Roche	Phase II (NCT04333914)
	Kevzara (sarilumab)	A human monoclonal antibody against the interleukin-6 receptor	Regeneron & Sanofi	Phase II (NCT04359901)
	Jakavi (ruxolitinib)	A Tyrosine kinase inhibitor antineoplastic agent	Novartis	Phase II (NCT04354714)
	Kaletra (lopinavir/ritonavir)	HIV protease inhibitor	AbbVie	Phase III (NCT04321174)
	Camostat mesylate	A protease inhibitor approved in Japan and Korea for chronic pancreatitis	Ono Ph.	Phase II (NCT04353284)
	RhACE2 APN01	RhACE2APN01 is a first experimental drug to treat COVID-19	Apeiron Biologics	Phase II (NCT04335136)
	IFX-1	A first-in-class monoclonal antibody targeting the complement activation product C5a	Inflarx	Phase II (NCT04333420)
Vaccines	mRNA1273	RNA vaccine made with messenger-RNA (mRNA) encoding the spike protein of SARS-CoV-2 encapsulated in a lipid nanoparticle	Moderna	Phase I (NCT04283461)
	NVX-CoV2373	Produced high levels of spike protein-specific antibodies that block the activity of ACE-2 and SARS-CoV-2	Novavax.	Preclinical trials
	Lentiviral Minigene Vaccines (LV-SMENP)	Designed to infect dendritic and T cells to induce immunity	SGIMI	Phase II (NCT04276896)
	BCG tuberculosis vaccine	Bacillus Calmette-Guérin tuberculosis vaccine that induces a broad innate immune-system response	MCRI	Phase III (NCT04327206)
	INO-4800	A DNA plasmid vaccine delivered into the skin via a patch-style electroporation device	Inovio Ph.	Phase I (NCT04336410)
	AD5-nCov	A recombinant adenovirus type-5 vector (Ad5) vaccine currently being investigated for prophylaxis against SARS-CoV-2	CanSino Biologics Inc	Phase I (NCT04313127)
	ChAdOx1	A potential vaccine against another human coronavirus, (MERS-CoV)	University of Oxford	Phase II (NCT04324606)
	BNT162	mRNA vaccine for COVID-19 infection	BioNTec & Pfizer	Preclinical trials
Convalescent Plasma	Convalescent plasma	Anti COVID-19 Convalescent Plasma	Orthosera Kft	Phase I (NCT04345679)
Miscellaneous	Cell Therapy (NKG2D-ACE2 CAR-NK cells)	NKG2D receptor for the immune system's natural killer (NK) cells paired with the ACE-2 receptor that the coronavirus uses to enter human cells	CPHMC	Phase II (NCT04324996)
	47D11	A human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV) in cell culture	-	-

Geno-Immune Medical Institute), (Murdoch Children's Research Institute), CPHMC (Chongqing Public Health Medical Center), Source: https://clinicaltrials.gov/; WHO

Drugs

Drug repurposing

The fastest way to fight the COVID19 pandemic is to find potential drug candidates among already-existing drugs, because existing drugs have established dosing and safety criteria, though use for a new indication may require alterations in dosing strategies. The knowledge base from prior clinical use minimizes the risk for unexpected untoward effects that might delay clinical progression as a COVID-19 therapeutic. This strategy is termed "drug repurposing" or "drug repositioning" and is used for using already approved drugs for curing novel/new infections for which there is none approved drug.[43]

The safety record of a known drug can, as discussed above, minimize risks of clinical failure and speed development. Both preclinical model data and human clinical or field use data can add insights regarding the feasibility of a new use. Drug formulation development, manufacturing capability, and even dug distribution avenues will all likely have been well-studied. Among drawbacks, the drug's efficacy had earlier been optimized for a different use, possibly to a formulation or even to a chemical entity that is not ideal for the new use, though it may provide a benefit. Because SARS-CoV-2 is known to undergo mutations in structure, its modest rate of genetic drift could confer treatment resistance. This phenomenon should be monitored with all treatment regimens.

Overall, the many advantages of drug repurposing make it more desirable than a *de novo* drug discovery approach when facing a pandemic situation, where speed to market of a safe and effective product is a huge consideration. Cost savings, though a lesser consideration, are another advantage. It is estimated that the average development cost of a repurposed drug is ~$300 million, compared to higher cost ($2-3 billion) of a completely new drug.[44]

In this section, some of the drugs that are already in use in China and Japan and are currently used in the United States for COVID-19 will be presented:

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an anti-malarial drug used also for treating lupus and rheumatoid arthritis. It has been reported to have antiviral activity in *in vitro* studies, wherein it appears to inhibit entry of SARS-CoV-2 into cells.[45] In a French study that has been at least temporarily withdrawn for revision, some patients with COVID-19 treated with HCQ recovered, but it was not known whether the drug was the cause. Dozens of clinical studies are currently underway in several countries.[46-48] Results of a new study published on May 22, 2020 in Lancet clarify that chloroquine/HCQ treatment is not as promising as expected. The study covers four groups of patients (chloroquine treatment, chloroquine + macrolides, HCQ or HCQ + macrolides) from 671 hospitals worldwide. During the study period (December 2019 to April 2020), 96,032 COVID-19 patients with an average age of 54 years were admitted to these hospitals. Among them, 14,888 patients were treated with the above treatment groups. The rest is used as a control group. Chloroquine was administered to 1868 patients, Chloroquine + macrolides were given to 3,783 patients, and 3016 were treated with HCQ and 6221 received HCQ + macrolides. Results were described as follows based on mortality: control group 9.3%, chloroquine group 16.4%, chloroquine + macrolide group 22.2%, HCQ group 18% and HCQ + macrolide group 23.5%. Similar results were reported for cardiac arrhythmias in hospitalized patients: control group 0.3%, chloroquine 4.3%, chloroquine + macrolide group 6.5%, HCQ group 6.15% and HCQ + macrolide group 8.1%.[49]

Remdesivir

Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerase and exhibits *in vitro* activity against SARS-CoV-2. Remdesivir was originally developed to fight RNA viruses, including respiratory syncytial viruses.[50] There are at least 13 ongoing remdesivir clinical trials in China, Europe and the United States. Preliminary results from a phase I study the United States show promise for treating COVID-19.[43] On 29th April, 2020, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), summarized the preliminary findings publicly, noting that in studies of over 1,000 treated patients, those who took remdesivir recovered approximately in 11 days, contrary to 15 days for those on placebo, a result that

reach statistical significance.[51]

Tocilizumab (Acterma)

Another commercial drug, acterma, is made by Roche and is also under evaluation for the treatment of COVID-19. It is a monoclonal antibody approved by the FDA for the treatment of immune "cytokine storms" caused by immune overreaction in rheumatoid arthritis and cancer patients.[52] Clinical trials of COVID-19 patients with this drug are reported to be underway in China, the USA, and in Europe, including a recently described French trial.[53,54]

Sarilumab (Kevzara)

Sarilumab is also a human monoclonal antibody vs. the interleukin-6 receptor. Originally, this drug was developed for the treatment of rheumatoid arthritis by Regeneron Pharmaceuticals and Sanofi, approved by the US FDA on May 22, 2017 and the European Medicines Agency on June 23, 2017. Trials are currently underway to target the "cytokine storm" immune response in severely ill COVID-19 patients, which seems to be a common theme for drugs considered for repurposing for curbing this pandemic. The initial results, published at the end of April, are suggestive of a benefit for the most critically ill patients. After reviewing the initial data showing that patients who are severely ill but who are not in serious condition experience little benefit, the company has announced that it will continue testing Sarilumab only in those patients who are critically ill.[55-58]

Ruxolitinib (Jakavi)

Ruxolitinib was developed by Novartis to treat infections and autoimmune diseases, and later developed as an atopic dermatitis cream. Mexico and Canada are going to test the drug in COVID-19 infected patients who have exhibited SARS symptoms associated with an immune response to a “cytokine storm”. Preliminary results are expected by June 2020. On April 7, 2020, the United States established a managed access program for use in severe COVID-19 patients.[59,60]

lopinavir/ritonavir (Kaletra)

Accvie's Keletra, an antiviral combination for the treatment and prevention of HIV, is currently under investigation in more than 20 trials worldwide for COVID-19. Initial results are expected in early May 2020. According to results released in March, there was no difference in viral load or 28-day mortality in trials randomized in China among 199 patients. The average clinical recovery time was one day lesser in patients who were administered the aforementioned drug. But the same doctors at Wuhan Jinvintan Hospital concluded that some of the COVID-19 patients treated with Kaletra and potassium bismuth citrate in April benefitted from treatment.[61-64]

Camostat mesylate

Camostat mesylate is a protease inhibitor used commercially in Japan and Korea to treat chronic pancreatitis. In an *in vitro* experiment, it was found to block entry of SARS-CoV-2 into human cells. In early April, approximately 180 COVID-19 patients aged 18 to 110 years were recruited from nine regions of Denmark, and phase 2a trials were conducted to investigate 30-day changes in disease in terms of severity and mortality. Their conclusions are expected by December 2020. The University of Tokyo has also released a trial plan for Camostat mesylate and related drugs nafamostat mesylate since early April 2020.[65-67]

RhACE2 APN01

Apeiron Biologics's RhACE2 APN01 is a recombinant human angiotensin converting enzyme 2 (rhACE2) protein is in phase II clinical trials of acute lung injury and pulmonary arterial hypertension. This synthetic protein may be used by SARS-CoV2 virus to enter cells and has been tested in Austria to block the viral influx of COVID-19 patients and reduce viral replication, thereby reducing the chance of death or mechanical ventilation. Preliminary results of the test are expected in September 2020.[68]

IFX-1

IFX-1 is a monoclonal anti-human complement factor C5a antibody designed to inhibit the biological activity of C5a. This drug is in clinical trials for Hidradenitis Suppurativa, ANCA related vasculitis and Pyoderma Gangraenosum. German biopharmaceutical company, InflaRx registered and dosed the first patient in an IFX-1 clinical study in Covid-19 with severe pneumonia in the Netherlands. The preliminary results are expected in late October 2020.[69,70]

Aspirin, Atorvastatin, Rivaroxaban, Omeprazole, and Clopidogrel

The Imperial College London started a trial of cardio

protective drugs to prevent direct damage to the heart muscle which appears to drive the severity of COVID-19 in certain patients, as well as their likelihood of needing invasive critical care. The trial included more than 3,000 patients in the UK and the estimated study completion date is March 30, 2021.[71]

Other screening efforts

Many compound collections in screening libraries worldwide contain clinically used drugs. And a variety of high-throughput assays can be used to find activity vs. COVID-19. No results have been published, though in informal online public presentations at least one effort has been summarized. Calibr, a drug discovery-focused subdivision of Scripps Research, has over several years built a large collection of >11,000 clinically used compounds and marketed drugs, a chemical library termed the ReFRAME collection. Dr. Arnab Chatterjee has indicated that many efforts are underway to define anti-COVID-19 activity for members of this library, which includes many of the drug repurposing candidates described above, such as remdesivir, so the activity of these candidates can be independently gauged and compared vs. other repurposing candidates. Preliminarily, Dr. Chaterjee reports that over two dozen library compounds show promise in one or more assays run at Calibr or by its collaborators. In addition, the team is evaluating several drug combination strategies. In a hypothetical example, an otherwise suboptimal dose of drug A and an otherwise suboptimal dose of drug B, given together, may provide a benefit beyond that of either drug used alone. Such a drug cocktail strategy is not at all unusual in therapy, and it may be possible to perhaps augment the efficacy of one agent (remdesivir, for example) by co-administration with a second drug. This lowering of dosage could widen therapeutic windows, augmenting the safety of a treatment regimen.

New chemical entities rather than repurposed drugs

The main drawback of the drug repurposing strategy that discussed above, is the drug itself was optimized for another purpose and is likely not ideal for the new use, though it may provide a measurable benefit. For example, an analog of remdesivir might be more active than remdesivir itself for COVID-19 therapy. A new chemical entity, however, begins near "square 1" in terms of drug development, especially regarding establishing a safe human dose, pharmacokinetic, and pharmacodynamics parameters. Thus, it will undoubtedly be slower to market, a key disadvantage in a pandemic situation. The main advantage, though, is that the end product is more likely to be optimized for efficacy vs. COVID-19. New drug discovery is less likely to make an impact on the pandemic, but should the disease become endemic, such treatments will be of higher value. As the progression of the disease is better understood at a mechanistic level, new targets will undoubtedly be identified that will spur drug discovery efforts, perhaps initially by a repurposing approach due to time pressure, but then also by systematically pursuing the discovery of new chemical entities.

Vaccines

A vaccine is a biological preparation providing active acquired immunity to a specific infectious disease. Typically, a vaccine contains an agent that closely related to the disease-causing microorganism, a virus in this case. The agent can be some form of biological material from the virus, such as a functional surface protein, or in other cases be either a weakened or killed form the entire infections agent. After administration of the vaccine, the human immune system recognizes the biological material to be foreign and develops specific antibodies to recognize and eliminate it.[98] Vaccines have revolutionized many aspects of human health, perhaps best exemplified by the eradication of smallpox in the 1970s, after the disease had claimed at least 300 Million lives earlier just in that same century. Curiously, however, anti-vaccination rhetoric has prompted significant opposition to vaccinations in general, which threatens the ability to establish and maintain herd immunity for a host of vaccine-preventable maladies. Continued education efforts are needed to combat anti-vaccination propaganda.

Over 10 groups are working on potential vaccines against SARS-CoV-2. Several of these groups are supported by the Alliance for Nonprofit Epidemic Innovation (CEPI). Currently, over 120 vaccines around the world are under investigation, with at least six already approved for human clinical trials.[72] Here, we discuss some of these candidate vaccines

which are in clinical studies.

mRNA1273

mRNA1273 by Moderna is an RNA vaccine made of messenger-RNA (mRNA) encapsulated in lipid nanoparticles and encoding the spike protein of SARS-CoV-2. Phase 1 trial of 45 infected patients aged between 18 and 55 in three regions of the US (United States) will evaluate the safety of the vaccine and will provide the initial data for an immune response. The completion of the test is expected on June 1, 2020.[73,74] Preliminary results of a phase 1 clinical trial were published on May 18, the company said the mRNA vaccine produced neutralizing antibodies in 8 healthy individuals out of 45 registered subjects. Phase two trials will include 600 participants from eight states and the screening for subjects has already begun.

NVX-CoV2373

NVX-CoV2373 produces high levels of neutralizing antibodies against SARS-CoV-2 in animal studies, and the first human phase I trial will start in mid-May.[75] Novavax said its Matrix-M adjuvant will be administered in conjunction with the vaccine candidate NVX-CoV2373 to enhance the immune response. According to the company, results from a preliminary trial of 130 adults are expected in July 2020.[76]

Lentiviral Minigene Vaccines (LV-SMENP)

The Shenzhen Geno-Immune Medical Institute has discussed their efforts to engineer minigenes encoding a viral antigen. Lentivir vectors, designed to induce immunity by infecting dendritic and T cells, deliver antigen. The test of 100 adults in Shenzhen, China, is expected to be completed later this year.[77]

BCG tuberculosis vaccine

The UMC Utrecht Bacillus Calmette-Guérin tuberculosis vaccine causes a wide range of innate immune system reactions that together prevents/protect against serious illness or infection from other respiratory pathogens. In large trials in Netherlands and Australia, BCG was shown to improve the immune defense of health workers, while older people reported reduced unplanned absenteeism from respiratory diseases. The same protective effects may extend to COVID-19 and is under investigation. Furthermore, 02 additional trials by the Max Planck Institute in Germany for the related tuberculosis vaccine candidate VPM1002 are also ongoing .[78,79] It should be emphasized that there is no evidence that BCG protects people from COVID-19 virus infection. Two more clinical trials are underway to address this issue and WHO will evaluate the evidence where possible. Without evidence, WHO does not recommend BCG vaccination to prevent COVID-19.[80]

INO-4800

Inovio Pharmaceuticals' INO-4800 is a DNA plasmid vaccine delivered via a patched electroporation device to the skin. INOVIO has announced that it expects to Phase 1 clinical trial results at the end of June 2020. Currently, 40 healthy volunteers are enrolled at the University of Pennsylvania site and in clinics in Kansas City, MO. Each study participant is to receive 2 doses of INO-4800. The Phase 1 study is designed to evaluate the safety and efficacy in terms of immunogenicity of INO-4800, a prelude to a Phase 2/3 efficacy trial. The company said it is capable of producing 1 million doses by the end of the year for further testing and emergency use.[81]

AD5-nCov

Ad5-nCoV is a recombinant adenovirus type-5 vector (Ad5) vaccine that is currently being under investigation for overcoming SARS-CoV-2 infection. In March 2020, CanSino Biologics Inc., in collaboration with the Beijing Institute of Biotechnology, announced the approval of a phase 1 clinical trial scheduled for completion in December 2020. In this study researchers will evaluate the antibody response in healthy patients between 18 to 60 years of age, the patients will receive one of three study doses, which will be followed up by observing the response at 2 weeks, 4 weeks, 3 months and 6 months after vaccination.[82]

ChAdOx1

ChAdOx1 nCoV-19 is another vaccine currently being studied for prevention of SARS-CoV-2 infection. The ChAdOx1 virus vector was developed by Oxford University and was investigated as a potential vector of vaccines against other human coronaviruses, MERS-CoV.[83] A Phase I / II randomized, single-blind placebo-controlled trial to investigate the safety, efficacy, and immunogenicity vaccine has been in progress since March 2020 and will be concluded of May 2021. The trial is conducted in the UK and the vaccine will be administered intramuscularly to healthy volunteers aged between 18 and 55.[84]

BNT162

The German company BioNTech, working collaboratively with the American pharmaceutical company Pfizer, has begun human trials of potential Covid-19 vaccines. Involvement of the global pharma giant Pfizer raises confidence for high production and distribution capabilities, should it prove successful. According to Mainz-based BioNTech, the first cohort of patients received the candidate vaccine named BNT162 in a Phase 1/2 clinical study in Germany, beginning on April 23, 2020, 12 study participants have to date been vaccinated in this study. Pfizer has announced that it will begin testing experimental vaccines in the United States in May 2020, and expects that an emergency use vaccine could be available in the fall.[85,86]

Convalescent plasma

Convalescent plasma is one of the older established methods for treating infectious diseases, dating back to the late 19th century. It relies on using plasma recovered from surviving COVID-19 patients to prompt an immune response in individuals in the midst of battling the disease. Antibodies from the donor plasma can, in principle, ameliorate at least some of the more serious disease symptoms, conferring passive immunity against the virus. Drawbacks include the finding that widely varying amounts of antibodies are produced in infected individuals, and with different rates of formation. Many pharmaceutical and biotech companies are focused on isolating donor plasma thought to have the greatest potential for neutralizing SARS-CoV-2. In China, Europe and the United States, controlled trials are underway to collect evidence of a therapeutic benefit. In another study, a group of 10 patients with severe illness in China, the results released in April showed a marked improvement over similar patients who did not receive treatment. Further studies may corroborate these findings.[87-90]

Miscellaneous

Cell Therapy (NKG2D-ACE2 CAR-NK cells)

Natural killer cells (NK) are distinctive lymphocytes that may act against dangerous infections. A clinical research is underway that is intended to assess the safety and efficacy of NK cells in conjunction with standard treatment for COVID-19-associated pneumonia. Chongqing Medical Health Center has started a multicenter phase 1/2 trial in 90 patients to test whether this cell therapy can inhibit entry and multiplication of cells of SARS-CoV-2. Furthermore, this study will be helpful in monitoring 28 day efficacy critical pneumonia COVID-19 patients.[91]

Antibody47D11

A recent article in Nature Communications disclosed a human monoclonal antibody named 47D11 that neutralizes SARS-CoV-2 (and SARS-CoV) in cell culture [92]. 47D11 links a preserved epitope on the spike proteins' receptor binding domain (RBD). 47D11 has cross-neutralization ability vs. SARS-CoV and SARS-CoV-2, using a mechanism independent of receptor binding inhibition. This antibody will be useful in developing antigen detection tests and serological tests targeting SARS CoV-2. Hence, this antibody either alone or together provides the possibility to prevent and/or treat COVID-19.

Conclusion

The COVID-19 pandemic impacting human activities worldwide with deleterious effects on human mental and physical health. The complicated structure of SARS-CoV-2 virus has captured the attention of the scientific community in various fields. The infection is diagnosed by the combination of clinical symptoms and laboratory tests. Various poi nt of care devices have been developed and approved by FDA to fight against COVIID-19. However, specificity and accuracy are major drawbacks for such devices. Hence, real-time ETPCR-based analyses are still the gold standard for COVID-19 detection. The development of anti-COVID-19 drugs is at the early stages. Scientists are focusing on the development of vaccines and promising results have been reported so far. The ultimate aim of such vaccines is providing a pathway to enhance acquired immunity on a global scale thereby reducing infection and death rate.

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