The emergence of the SARS-CoV-2 strain of the human coronavirus has thrown the world into the midst of a new pandemic. In the human body, the virus causes COVID-19, a disease characterized by shortness of breath, fever, and pneumonia, which can be fatal in vulnerable individuals. SARS-CoV-2 has characteristics of past human coronaviruses, with close genomic similarities to SARS-CoV, the virus that causes the disease SARS. Like these related coronaviruses, SARS-CoV-2 is transmitted through the inhalation of droplets and interaction with contaminated surfaces. Across the world, laboratories are developing candidate vaccines for the virus—with vaccine trials underway in the United States and the United Kingdom—and considering various drugs for possible treatments and prophylaxis. Here, we provide an overview of SARS-CoV-2 by analyzing its virology, epidemiology, and modes of transmission while examining the current progress of testing procedures and possible treatments through drugs and vaccines.

Introduction

Near the end of 2019, cases of an unknown upper respiratory tract infection began appearing in Wuhan, Hubei Province, China [1]. The illness spread rapidly throughout the city and eventually to the entire country, with scientists and doctors having no answers or solutions for its transmission or pathology. By early January 2020, it was determined that these infections were caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), with the disease being named COVID-19 (coronavirus disease 2019) [2,3].

Global efforts to contain the virus were mixed, with some countries and/or communities enacting stricter actions than others [4,5]. As a result, the virus soon found its way around the world, and by the beginning of March 2020, the World Health Organization...
other coronavirus strains that have been identified in
identified: HCoV-HKU1 and HCoV-NL63 [16]. Three
first two coronavirus strains, two other strains were
have low levels of severity. After the emergence of the
common cold, and infections caused by the viruses
common upper respiratory tract diseases, such as the
HCoV-OC43 [15]. These viruses were found to cause
population were human CoV-229E (HCoV-229E) and
3 000 000 kilobases) [14].
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humans [13]. In general, they are classified as single-
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found only to cause mild illnesses; however, research
three severe coronavirus strains, infections from the
severe strains of coronavirus is their extremely low
HCoV-C43, HCoV-HKU1, and HCoV-NL63 from the
Severe strains of coronavirus are defined as having high
ly infectious, and new strains have proven otherwise [22].
WHO) officially labeled the disease as a pandemic [6].
Unprecedented measures were taken to slow the
spread – major cities and even entire nations imple-
mented lockdowns, restrictions on travel and gatherings,
and closures of businesses and schools [7]. All
these measures have stifled financial and economic
confidence, sparking fears of a global recession.
As the numbers of infections and deaths from
COVID-19 exponentially rise each day, it is imperative
to understand the workings of SARS-CoV-2 and the
possible treatment routes to combat this latest pan-
demic. Here, we compare SARS-CoV-2 to previous
coronaviruses in terms of epidemiology and molecular
biology, discuss current and prospective testing mecha-
nisms, evaluate the currently available and novel treat-
ments for COVID-19, and provide details on the types
of potential SARS-CoV-2 vaccines under development.
Additionally, while not a topic of this review, the
immunopathogenesis of COVID-19 has been studied
extensively [8].

History of coronaviruses

Unlike viruses such as influenza, smallpox, and polio,
coronaviruses have only recently been discovered to
infect the human population. When they were first dis-
covered in the 1960s, there was almost no epidemi-
ological, genomic, or pathogenic information about
these viruses – only that they contained RNA sur-
rrounded by a membrane composed of ‘spike’-shaped
proteins [9]. The crown-like appearance of these sur-
facial ‘spike’ proteins gave the virus family the name –
‘corona’ being Latin for crown [10]. Viruses with that
specific shape and structure belong to the family of
Coronaviridae, which are grouped into four genera
using their phylogeny: alpha-CoV, beta-CoV, gamma-
CoV, and delta-CoV [11,12]. As of 2020, the US-based
Centers for Disease Control and Prevention (CDC)
recognizes seven coronavirus strains that can infect
humans [13]. In general, they are classified as single-
stranded, positive-sense RNA genome-bearing viruses
[12]. Their genome is estimated to be around 26–
32 kilobases (for comparison, the human genome is
3 000 000 kilobases) [14].
The first identified coronaviruses in the human
population were human CoV-229E (HCoV-229E) and
HCoV-OC43 [15]. These viruses were found to cause
common upper respiratory tract diseases, such as the
common cold, and infections caused by the viruses
have low levels of severity. After the emergence of the
first two coronavirus strains, two other strains were
identified: HCoV-HKU1 and HCoV-NL63 [16]. Three
other coronavirus strains that have been identified in
the human population since are SARS-CoV, MERS-
CoV, and SARS-CoV-2 [13]. All three of these coron-
avirus strains vary from the four common strains as
they can cause severe illnesses that may result in
death.

One characteristic that distinguishes HCoV-229E,
HCoV-C43, HCoV-HKU1, and HCoV-NL63 from the
severe strains of coronavirus is their extremely low
basic reproduction numbers (R0) [17]. The basic repro-
duction number is used to describe how transmissible
or contagious a pathogen is [18]. The value is not fixed
and can be affected by intervention methods such as
social distancing and vaccination. The R0 value is used
to signify the potential amount of people a single
infected person can infect [19]. The higher the R0 num-
ber is, the higher the chance that infected individuals
will spread the pathogen to others. Thus, pathogens
that are deemed extremely infectious have R0 values
greater than 1, while some pathogens that have low R0
values can be contained without any need of isolation
of known cases and potentially infected individuals
[20].

While coronaviruses have only been known in the
human population for six decades, they have come to
the forefront of research and news due to the outbreak
of SARS-CoV [12], which demonstrated in the early
2000s that this virus family has the potential to cause
a pandemic [21]. The four common, nonsevere human
coronaviruses are distributed globally, with a low den-
sity in any given local population [12]. Regarding the
three severe coronavirus strains, infections from the
SARS-CoV strain were localized in China, with small
outbreaks in other countries. MERS-CoV infections,
which have been ongoing since 2012, are localized in
the Middle East. SARS-CoV-2, which causes COVID-
19, is a global pathogen of pandemic proportions.
When first discovered, human coronaviruses were
found only to cause mild illnesses; however, research
and new strains have proven otherwise [22].

Rise of pathogenic coronaviruses

Between SARS-CoV, MERS-CoV, and SARS-CoV-2,
the former two have been extensively studied and do
not pose a significant global threat at the moment;
however, there is still much to learn about SARS-
CoV-2.

SARS-CoV

The SARS-CoV strain emerged in November of 2002
in Guangdong Province, China. The strain causes the
disease severe acute respiratory syndrome (SARS),
with common symptoms of infection being fever, cough, chills, and fatigue [23]. Many of the cases also exhibited shortness of breath and the development of pneumonia [23]. Fatal cases ended in respiratory distress and lung failure [24]. Patient outcomes were affected by host factors such as pre-existing conditions and age. The SARS-CoV strain was found to have an incubation period of 2–10 days [25]. It specifically targets the epithelial cells in the respiratory tracts causing damage throughout the organ, especially in the alveoli [26].

Before its containment, SARS cases were reported in 26 countries, with a majority of the cases concentrated in China [27]. At the height of the epidemic, there were approximately 8000 cases with 774 deaths reported [27]. Social distancing and traveler screening were used to mitigate the outbreak [28]. The virus is thought to have originated from palm civet cats, which suggests that there was a zoonotic shift to the human population [29]. SARS cases have been dormant since 2004 when the last naturally occurring case was reported. Quarantine measures and isolation led to the control of the SARS pandemic [30].

**MERS-CoV**

In 2012, a betacoronavirus emerged as the second pathogenic coronavirus in the human population and originated in Saudi Arabia in September 2012 [31,32]. This strain of betacoronavirus is currently the most lethal strain, with a mortality rate of ~32–33% [12]. Twenty-seven countries have reported cases of Middle East respiratory syndrome (MERS) caused by this virus, MERS-CoV, with 80% of these cases occurring in Saudi Arabia. As of January 2020, there have been 2519 cases of MERS with 866 associated deaths [33]. There is evidence that MERS originated from camels and spread to humans via a zoonotic shift [34]. The incubation period of MERS is approximately 5–6 days; however, symptoms can persist from anywhere between 2 and 14 days [35]. Symptoms include fever, cough, and shortness of breath. More severe cases of the viral infection developed pneumonia and kidney failure.

Similar to SARS, patient outcomes were affected by host factors such as medical history and age. There were higher levels of mortality associated with patients that had a pre-existing medical condition which weakened their immune system [33]. Quick quarantine and isolation led to the control of the MERS pandemic [36].

**SARS-CoV-2**

On December 31, 2019, the first case of COVID-19 in Wuhan, China, was reported to the WHO. On March 11, 2020, the virus was declared a global pandemic. As of April 2020, coronavirus has affected 214 countries and territories, spreading extremely quickly (Fig. 1) [37]. There are over four million cases of COVID-19 worldwide and over 270,000 deaths [38]. Similar to SARS and MERS, patient outcomes are affected by factors such as pre-existing conditions and age. China’s authorities reported that the highest mortality rate was for those above 80 years of age [39]. Although the origin of this pandemic is uncertain, it is widely believed that the disease spread from bats, which act as intermediate hosts between the virus and humans; this idea is being tested in ongoing research [40]. Additionally, there is a possibility that pangolins were the intermediate between bats and humans for SARS-CoV-2 transmission [41]. There is no evidence that this virus was made in a laboratory, and the overwhelming evidence suggests a zoonotic shift from animals to humans [42]. The incubation period of COVID-19 can be up to 2 weeks with a median of 5 days; during this period, the virus can be transmitted to others [39].

Symptoms of the virus are similar to MERS and SARS and include fever, cough, and shortness of breath [39]. COVID-19 is significantly more infectious than SARS and MERS in terms of human-to-human transmission, causing the number of cases to skyrocket before the development of symptoms, making it harder to isolate and control [46].

**Epidemiology of SARS-CoV-2**

In over 80% of cases of COVID-19, symptoms present as a mild fever, dry cough, and shortness of breath. Severe cases displayed symptoms such as dyspnea (shortness of breath) in 44% of patients, hypoxia (oxygen depletion in body tissues) in about 50% of patients, and a high fever in around 14% of total patients [47–50]. Depending on the age, hospitalization rates in the United States range from 0.1% for ages 5–17 to 17.2% for ages 85 or above with 5% of total cases experiencing critical conditions such as shock.
and multi-organ failure [47,51]. There are two main clinical symptoms that appear for critically ill patients with COVID-19: low levels of oxygen due to poor breathing (acute respiratory distress syndrome) and fevers [52,53]. This lack of oxygen is usually addressed through mechanical ventilation in non-COVID-19 patients [54]. Additionally, it is thought that later phases of COVID-19 bring a lack of oxygen due to low lung compliance and sedation has been suggested in support of mechanical ventilation due to the large demand of drugs such as oxycodone and hydromorphone [54–57].

However, in some cases, those confirmed with COVID-19 are asymptomatic yet can still spread the disease [58]. For this reason and the long incubation period of up to 2 weeks, COVID-19 has demanded extreme safety precautions to be implemented to minimize transmission and morbidity. This ‘flattens the curve’ of the projected number of infections and aims to stop healthcare services to be overwhelmed with so many new cases at once. Such precautions include social distancing (upholding 2 m distance from others), which would reduce the median estimated number of infections by 78% by some models [59,60]. Despite the implementation of these measures, many countries are still experiencing infections at an exponential rate.

Notably, infection and death rates are not the same between countries, age-groups, or even races [61]. Despite the worldwide mortality rate of 6.9%, death rates range from ~0.1% in Chile and Israel to 14% in Italy (note these are estimates based on numbers reported by the WHO as of May 8, 2020, and do not take account for asymptomatic or those infected who have not been tested) [44]. Countries are in various stages of their outbreaks, but there are still many factors that lead to the infection and death rate disparity such as population density, healthcare system, testing policy, and age structure of the country. Testing alone has proved to be a major determinant of the success of a country’s response to this outbreak. The decision on whether to engage in mass testing has contributed to the quick control of the outbreak in countries such as Germany and South Korea, whereas the reluctance to provide mass testing of those exhibiting symptoms of infection done in the UK and United States has, arguably, prolonged the outbreak [62,63]. A nation’s testing system is especially pertinent given the possibility of disease transmission through asymptomatic carriers [64].

Moreover, the severity and onset of COVID-19 vary dramatically for different ages with worsening symptoms with age [65]. The lowest risk is observed in those under 19 years of age with a mortality rate ranging from 0% to 0.1%, whereas those between 75 and 84 years of age have mortality rates ranging from 4.3% to 10.5%. The highest risk is seen in those aged...
85 or above, with a mortality rate of 10.4–27.3% [65]. Underlying health conditions including diabetes, cardiovascular disease, or a suppressed immune system also increase the fatality rate [66].

Considering its high mortality rate in certain groups and high transmission rate, without proper treatment, the thousands of reported deaths from this virus might turn into millions without a coordinated and strategy-based, worldwide response.

**Structure of SARS-CoV-2**

Like other coronaviruses, SARS-CoV-2 is a single-stranded, positive-sense RNA virus that uses spike proteins to bind to human lung epithelial cells (Fig. 2) [67]. The structure of the receptor-binding region that the virus binds to, the angiotensin-converting enzyme 2 (ACE2) receptor (Fig. 3), is the same target of the SARS-CoV outbreak of 2003 [68]. It is these receptors that act as docking sites for the spike proteins of SARS-CoV-2 to bind to, allowing the viral and cellular membranes to fuse (Fig. 3). From there, the virus ‘hijacks’ the cell; it integrates its RNA into the cell’s own replication machinery, facilitating propagation of the virus. The virus is then able to proliferate throughout the body, creating immune responses, and causing the person to become infected [69,70].

A commonality among coronaviruses is the use of their envelope-anchored homotrimeric spike glycoprotein (S protein) to mediate binding with host cell receptors (Fig. 3) [71]. The S protein is cleaved into two subunits during cell infection – the S1 subunit, which contains two receptor-binding domains (RBDs) that allow the virus to bind to its host cell, and the S2 subunit, which is critical for membrane fusion [72].

The host cell receptor for the S1 subunit of the S protein, ACE2, is a transmembrane protein located on the cells of epithelial tissue in the lungs, heart, kidneys, and intestine [73]. Its primary physiological function is to regulate the maturation of the peptide hormone angiotensin, which helps regulate vasoconstriction and blood pressure [74]. Thus, the expression of ACE2 has anti-inflammatory effects that can protect against lung injury, while its downregulation by the binding of SARS-CoV or SARS-CoV-2 has pro-inflammatory effects, which promote the severe acute lung injury symptomatic of infection by these viruses [75,76]. Beyond its potential role in the pathology of COVID-19, this receptor is directly linked to the infectivity and transmissibility of the SARS-CoV-2 virus. The fact that infectivity and transmissibility of SARS-CoV-2 are higher than those of SARS-CoV is a result of the 10- to 20-fold higher binding affinity of the SARS-CoV-2 spike glycoprotein (red) to the ACE2 receptor (green) of host cells compared to the SARS-CoV spike glycoprotein (red) binding to the ACE2 receptor [77].
CoV-2 RBD to the ACE2 receptor due to differences in the amino acid sequence of the SARS-CoV-2 RBD region which allow more interactions between the S protein and the host cell receptor [77,78]. The binding affinity of the virus to host cell ACE2 receptors also dictates the pathway of intermediate host organisms that the virus could infect before being transmitted to humans and, therefore, which organisms could be used to study the virus [79,80].

After the S1 subunit binds to the ACE2 receptor of the target cell, the heptad repeat 1 (HR1) and 2 (HR2) domains of the S2 subunit combine to create a six-helix bundle core that brings the viral and host cell membranes within close proximity of each other for fusion to take place [80,81]. Upon membrane fusion, the RNA of the coronavirus genome is released into the host cell cytoplasm via an early endosome – unlike SARS-CoV, which employs a late endosome and therefore must cross higher barriers of antiviral host immunity – where it is translated into a replication–translation complex that in turn translates subgenomic RNA into accessory and structural proteins (Fig. 3) [82–84]. These proteins form viral particle buds that are exocytosed to spread the virus to surrounding cells, thus spreading the infection throughout the host organism.

**Mechanism of infection**

Between infected hosts, COVID-19 is primarily transmitted through contact with droplets that contain viral particles [85]. Droplets are any medium in which a human can release the virus, such as coughs, sneezes, and mucous. They generally cannot travel more than 2 m from their origin, though simulations investigating the effects of aerodynamics on the spread of these droplets suggest that fast physical activity, such as running or cycling, increases the distance they can travel [86,87]. While it is generally thought that droplets do not linger in the air, in one study, SARS-CoV-2 was found to last in the air for 3 h in experimental conditions [88]. This disease can also spread by a person touching contaminated surfaces then subsequently touching their facial area (fomite-mediated transmission). Depending on the material, the surfaces were shown to be infectious from several hours on cardboard to 3 days on plastics or stainless steel [88]. Despite these similarities to previous outbreaks and viruses, the ability of SARS-CoV-2 to stay on surfaces and affected individuals to not immediately display symptoms has made it difficult to contain and trace the virus, leading to the current global situation.

An understanding of the molecular mechanisms of this virus not only explains its increased transmissibility and the subsequent symptoms of infections, but also opens the door for a wide range of testing and treatment mechanisms that target the entry mechanism or epitopes of the virus.

**Testing for the virus**

**RT-qPCR-based tests**

The most prevalent form of testing right now utilizes quantitative reverse transcription–polymerase chain reaction (RT-qPCR) [89]. This form of testing is widely used to combat the outbreak in places such as the United States, Hong Kong, Germany, Italy, and South Korea [90–92]. The test requires a nasopharyngeal swab to gather genetic material that will reveal whether or not the patient has the virus. The testing mechanism first requires the isolation of RNA and then the production of a single-stranded complementary DNA (cDNA) copy of the RNA [93]. Finally, PCR is performed to amplify the cDNA for analysis, which, in all, takes hours to complete [94].

An important consideration for this testing method is navigating potential false-negative and false-positive results, which generally result from sample contamination [95]. In some instances, cases that have been suspected to be positive for COVID-19 via computed tomography (CT) images were not diagnosed as positive by RT-qPCR [95]. China has employed a high-resolution CT to supplement their testing to ward off false negatives [96].

The challenge with carrying out this procedure on a global scale is that the current supply for swabs is limited and hard to distribute. Swab production facility locations can lead to delays and shipment issues, inhibiting the volume of testing [6]. Some countries, including the United States and Iceland, are struggling to find suppliers that will provide authorized nasal swabs for mass testing [97].

Recently, molecular testing has been made more accessible to organizations that are outside of the traditional hospital setting through the US-based biotechnology company Abbott and the German technology company Bosch Healthcare Solutions. The Abbott RealTime SARS-CoV-2 Assay, which is their new automation systematic machine, reduces processing time from a few days to 15 min, because it reduces hands-on time and increases patient analysis flexibility. Each test conducted for this machine is one cartridge and each cartridge elicits one test, which means that there will be a low throughput [98,99]. The Vivalytic
VRI (viral respiratory tract infections) COVID-19 Test System pioneered by Bosch and Randox Laboratories is similar to the Abbott RealTime SARS-CoV-2 Assay in that it reduces hands-on time and can confirm a positive test within 2.5 h with a reported 95% accuracy [100].

Serological tests

One of the most common and fastest forms of testing is the lateral flow immunoassay, which takes a genetic sample from the patient and measures whether or not they have antibodies against a virus [101]. This test, however, is not for determining whether the patient has the disease currently, but instead, it measures whether an individual has antibodies for a disease, which would indicate that they have mounted an immune response against the pathogen in the past. Companies like Abbott also have antibody test, and recently, England has approved a serological test pioneered by the Swiss biotechnology company Roche Diagnostics [102,103]. Serological tests have a much higher success rate with these companies both boasting successes above 99% accuracy [104].

Another viable option is the enzyme-linked immunosorbent assay (ELISA)-based testing, because it is sensitive and is amenable to high-throughput assays [105]. However, some of these serological assays introduced early in the pandemic lacked specificity, which may result in the generation of false positives, leading to overestimates of rates of infection [106]. More specific assays have now emerged that are proving very useful in providing a fuller picture of the rates of asymptomatic or mild SARS-CoV-2 infection, through detection of antiviral antibodies that persist for months and even years after the virus has been cleared [107].

Altogether, serological tests can serve as an indicator for how widespread the virus is, while RT-qPCR tests can show who currently has the disease.

CRISPR-based testing

Clustered regularly interspaced short palindromic repeats (CRISPR) technology has promise as a tool for disease detection [108]. Two enzymes that work in conjunction with CRISPR, Cas13 and Cas12, can be activated when specific sequences of RNA are detected. Once the enzymes are activated, they exhibit local RNase or DNase behavior, respectively, breaking down strands of RNA or single-stranded DNA nearby; in a test scenario, this is usually measured with a fluorescent signal or activity on a lateral flow strip, which acts similarly to a pregnancy test. If the CRISPR-Cas complex is combined with a reporter molecule, the enzyme breaks down the nearby reporter molecule, triggering a response.

When Cas13 is used, a process called SHERLOCK can detect the presence of an RNA virus such as SARS-CoV-2 [109]. Cas13 is activated when it is guided to the specified sequence and starts to break down nearby RNA strands. When a RNA sequence reporter molecule is combined with the CRISPR-Cas13 sequence, Cas13 will break it down, signaling the presence of a specific RNA strand, such as a virus, through fluorescence or a lateral flow strip. Cas12 can also be used in a process very similar to SHERLOCK, called DETECTR, that shows the presence of a virus by activating Cas12 to break down a DNA-based reporter molecule [110]. DETECTR technology is faster than SHERLOCK, but both are being researched and tried as future testing methods. Recently, the company Sherlock Biosciences has received FDA emergency use approval (EUA) for its SHERLOCK-based COVID-19 test, which the first EUA with CRISPR technology [111].

Drug development for the treatment of COVID-19

Currently, there is no available cure or vaccine for COVID-19 and the fastest timescale for development of a vaccine is estimated to be between 12 and 18 months [112]. In the absence of these long-term and sustainable treatments, doctors and healthcare professionals are working on managing critical respiratory symptoms (dyspnea and hypoxia) from COVID-19 through the use of mechanical ventilation [113]. In a case study on 2634 hospitalized patients in New York, about 12% of the patients required ventilation and the mortality among those receiving ventilation was 88% [113]. The repurposing of drugs has also shown promising results for a possible treatment of COVID-19 symptoms: The WHO has outlined four drugs as potential therapeutic candidates for COVID-19 in their Solidarity Project: remdesivir, lopinavir/ritonavir, interferon beta-1a, and hydroxychloroquine/chloroquine [114]. Of these, remdesivir currently shows the most promise [115]. However, further studies have shown the promise of other drugs – EIDD-2801 and favipiravir [116,117]. Analyzing the pathways of these drugs not only provides a greater depth of understanding of the virus, but also reveals possible targets for the creation of an antiviral drug.
Remdesivir
A drug originally created to be used against the Ebola virus, remdesivir has recently been discovered to be effective in preventing the proliferation of SARS-CoV and MERS-CoV [115]. The structure of remdesivir prevents the propagation of viruses by blocking a crucial piece of RNA duplication machinery – the RNA-dependent RNA polymerase (RdRp) [118].

In a study of remdesivir, the drug was administered to mouse cell lines infected with SARS-CoV, MERS-CoV, and SARS-CoV-2 and was able to inhibit the spread of the SARS-CoV-2 virus [115]. For this reason, there is excitement about the potential of this drug. Currently, several phase II/III trials are underway with one highly powered (large sample size) trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) in the United States, reporting patients had a 31% faster time to recover when taken compared to a placebo [119,120]. This has been one of the few trials highly powered with a use of a placebo to generate positive results leading to its emergency authorization use by the FDA [121]. As a result, remdesivir has become one of the most promising drugs to fight COVID-19, being tested around the world by countries such as China, Germany, Italy, and South Korea, among others [122]. Further studies and results will be needed to determine its efficacy.

Favipiravir
Favipiravir (also known as Avigan) similarly selectively inhibits RdRp through preventing it from binding to its energy source (ATP), thus making it nonfunctional [118]. Its efficacy is promising, with China’s Science and Technology Ministry calling it an ‘effective treatment’ with ‘a high degree of safety’, as many symptoms such as fever and cough subsided quicker when taking the drug [122]. Even given these positive results, Japan is one of few countries heavily evaluating the drug with Fujita Health University performing phase II trials on the drug [122].

Hydroxychloroquine/chloroquine
Hydroxychloroquine and chloroquine are two safe, inexpensive drugs known mainly for their FDA-approved treatment against malaria and autoimmune diseases, but also have been found to have antiviral activity [123,124]. Viruses usually enter the body and infect cells through endocytosis, which packages the virus and brings it into the cell via an endosome. However, hydroxychloroquine/chloroquine increases the endosome’s pH, making it too basic for other viruses to survive and replicate [115]. Given its hydrophobic structure, the drug can circulate throughout the blood and the effects can spread throughout the body including the lungs, making it a strong candidate for treatment against COVID-19 [115]. Tests of hydroxychloroquine and chloroquine against COVID-19 in China and France have proven promising but only studied small sample sizes [125].

Nevertheless, due to the minimal known side effects of the drug, the FDA has authorized for emergency use by healthcare professionals [126]. There are future hopes that this is a drug that everyone could take to prevent COVID-19 (prophylaxis approach) and federal regulators in the United States have removed many regulations that have allowed for testing to hit ‘warp speed’ [127]. However, there are other studies suggesting no/limited effect of chloroquine, or even severe side effects [128–131]. Some hospitals have also stopped using this drug for these reasons.

Lopinavir/ritonavir
Lopinavir and ritonavir, referred to as Kaletra when combined, are mainly used to combat human immunodeficiency virus (HIV) infection by acting as a protease inhibitor that would prevent the cutting of certain proteins needed for HIV replication [132]. After initial reports of success from China and South Korea, scientists were excited by the potential of lopinavir/ritonavir as a treatment against COVID-19 [133]. Yet, when tested on hospitalized infected adults in isolation from other drugs, lopinavir/ritonavir showed no significant benefit/improvement, indicating that the protease inhibition was not the same for SARS-CoV-2 as for HIV, ceasing future testing of the drug [132,133].

Interferon beta-1a
Interferons are a natural component of the immune system that activate antiviral machinery in order to inhibit replication and increase immune response [134]. This process can be sped up via interferon injection [134]. Given its ability to stimulate active immunity, previous studies have tested alpha- and beta-types of interferons against MERS and SARS [135]. It was identified that the type 1 interferon of a beta-subtype was most effective against coronaviruses as it upregulates anti-inflammatory cells in the lungs [135]. Early testing of interferons in human epithelial cell lines showed a reduction in viral concentration by injection and a reduction in infection rates by administration of...
interferons by spray, in support of interferon-based prophylaxis [135,136]. Currently, interferon beta-1a is a specific type of interferon available in the market to help mitigate the symptoms of multiple sclerosis, but further research is needed to see its effects in humans [135].

**EIDD-2801**

EIDD-2801 can both serve as a preventable and treatable medicine through oral intake. In contrast to remdesivir, which may treat COVID-19 by inhibiting RdRp [102], EIDD-2801 induces lethal mutagenesis by accumulating deleterious transition mutations in the viral RNA while having many off-target effects [116]. The results of EIDD-2801 have shown the greatest promise out of all these drugs, having been shown to reduce the concentration of SARS-CoV-2 as well as other coronaviruses (MERS and SARS) when taken prophylactically [116]. While these results have only been observed in mice, its ability to be easily taken orally and as a potential preventative treatment makes it a strong candidate for continued research. As of April 7, 2020, the FDA has given the company responsible for EIDD-2801 approval to perform human trials [137].

Overall, the antiviral activities of these drugs, with the exception of lopinavir/ritonavir, have shown some level of efficacy against COVID-19 using different pathways. EIDD-2801, remdesivir, and favipiravir all mitigate SARS-CoV-2 by stopping the RNA-dependent RNA polymerase from replicating the virus further. By contrast, hydroxychloroquine/chloroquine targets endosomes, while interferon beta-1a takes advantage of the body's innate immunity increasing inflammatory responses. Trying to evaluate the level of success of these drugs against COVID-19 is difficult due to their different points of research; however, remdesivir is one of the few drugs to have a high-powered experiment that favors positive results, which has led it to become one of the more promising and frequently tested drugs around the world [122]. While there is no definite answer yet, testing of these drugs has garnered greater understanding of the viral mechanism that could further aid other drug repurposing or synthesis for a possible cure.

**Other possible treatments for COVID-19**

**CRISPR**

Along with possible drugs, new technologies have been utilized preemptively to counter the symptoms of SARS-CoV-2. CRISPR-Cas13 has been utilized to target essential parts of the SARS-CoV-2 virus, through an approach called PACMAN (Prophylactic Antiviral CRISPR in huMAN cells) [138]. Similar to SHERLOCK-based virus detection, PACMAN utilizes Cas13, which has RNase activity that can be used for both the detection (see above) and the destruction of SARS-CoV-2 (Fig. 4) [139]. This aspect of Cas13 can be utilized to destroy the virus with pinpoint accuracy, while also knocking out the RdRps. The main roadblock to using this technology is delivery. Some of the problems associated with the delivery of CRISPR-Cas13 have been researched, and possible liposomal delivery systems have been established [138]. While these treatments still require further testing, there is promising research in the use of CRISPR as a means of targeting the virus and stopping symptoms, as well as utilizing PACMAN to prevent future pandemics.

**Antibodies**

While antibodies indicate that a person has developed an immune response to the virus, there is no evidence that shows how long the person will be protected, if they are protected at all, from reinfection of COVID-19. However, in a study of 23 patients that recovered from COVID-19, it was found using ELISA that antibody concentration was associated with neutralizing activity [140]. This has led healthcare professionals to consider blood transfusion of convalescent plasma as a possible treatment. In a case study of five critically ill patients treated with plasma, four out of the five patients exhibited normalized body temperatures and decreased viral load, suggesting that the antibodies have antiviral activity [141].

Using ELISA, scientists from Utrecht University in the Netherlands were able to identify a reactive human monoclonal antibody (47D11) that blocks SARS-CoV-2 infection [141]. Similar to the antibodies found in the blood plasma transfusions, 47D11 antibody is able to reduce viral activity, while also having the capability to be synthesized in a laboratory. This leads to significant advantages compared to plasma as nothing has to be stored and there is not a limit to availability. With the recent evidence of 47D11’s efficacy in cells, pharmaceutical companies are in a rush to produce a monoclonal antibody treatment as the world waits for an answer.

**Vaccines against SARS-CoV-2**

The vaccine development process is known to take years for full approval for mass production. However,
many leaders in this area such as Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases, have recently suggested that this process could take less than a year given the current need to combat COVID-19. Meanwhile, researchers at Oxford University’s Edward Jenner Institute for Vaccine Research have started testing a vaccine in humans and could have results of its efficacy by June [142,143]. For most vaccines, this rapid progression would be seen as unrealistic, but the pressure needed to put this pandemic to halt has led to many regulatory agencies to speed up their approval process.

Typically, vaccine trials are three-phase processes that are run over the course of several years. The first phase is meant to assess the safety of a vaccine, and so, it is injected into a small group of healthy volunteers. Next, in the second phase, the efficacy of the vaccine is tested in several hundred volunteers, including at-risk groups. Finally, the third phase moves to testing in thousands of patients if the results are promising, and only then can a vaccine be mass-produced. However, governments worldwide have encouraged companies to launch production of vaccine candidates despite the fact that none of them have completed the clinical trial process [144]. There are several different types of vaccines that scientists are researching to combat COVID-19.

**Live vaccines**

This type of vaccine aims to provoke an immune response in vaccinated people by introducing a weakened version of the virus into their bodies. These live, attenuated vaccines are the closest thing to a natural infection, and so, they are very effective at creating an immune response [145]. The vaccines for measles, mumps, and chickenpox use this approach. However, children and immunocompromised individuals can have difficulties handling the live attenuated vaccines and evoking an immune response [146].

**Inactivated vaccines**

Another method of vaccination is to use a dead or inactivated virus, like in the polio vaccine. One upside to these vaccines is that there is no concern about the virus regaining pathogenicity and causing disease. However, booster shots are needed for continued protection because these vaccines trigger smaller immune responses [147].

**Subunit vaccines**

Rather than including the entire virus, subunit vaccines work by including only parts of the virus’ structure or subunits [148]. For example, a subunit vaccine for a
coronavirus strain may only include the S protein or parts of the S protein (Fig. 2). Similar to the inactivated vaccine, side effects are less common but booster shots are needed. Additionally, subunit vaccines may not be the most cost-effective method of acquiring immunity against the coronavirus since their production is very costly.

**Nucleic acid vaccines**

The previously mentioned approaches to vaccine development are labor-intensive and require scientists to work long hours cultivating and modifying the specific virus in the laboratory. Due to the urgency for a SARS-CoV-2 vaccine, researchers are trying novel approaches to vaccine development, with one such being a nucleic acid vaccine.

One of the first COVID-19 vaccines to be approved for clinical trials was a RNA vaccine first tested in Seattle [149]. Rather than injecting a weakened or other altered forms of the virus into patients, this vaccine works by injecting mRNA directly into the patient. The mRNA then codes for viral proteins that would lead to an immune response from the body and thus giving individual protection from the disease should they come into contact with the virus again. Other types of nucleic acid-based vaccines code for material that interferes with protein translation that is essential to the virus’ propagation [150]. However, despite the fact that this technology has been around for about 30 years, nucleic acid vaccines have not yet earned approval since an effective delivery system is needed in order for these vaccines to match the efficacy of a live vaccine [151].

**Viral vector vaccines**

In clinical trials, research is also being conducted for viral vector vaccines for COVID-19 [152]. In this particular vaccine, scientists engineer nonpathogenic viruses – or a viral vector – with the particular sequence that codes for the virus’ antigen. This approach is being used by researchers at Oxford University, who engineered a nonreplicating chimpanzee adenovirus with the spike sequence of the SARS-CoV-2 spike protein [153]. This vaccine is particularly promising since it can elicit a strong immune response [154]. However, patients may have pre-existing immunity to the vector, rendering the vaccine useless.

Even with all of these options available, developing a vaccine that can be distributed in mass to combat COVID-19 is not without its challenges. Vaccines are developed from scratch for each target, and vaccines against similar coronaviruses cannot be simply repurposed for new uses.

It is important to note that while vaccines were developed for both the SARS-CoV and MERS-CoV outbreaks, they were not utilized in the public sphere because they did not complete clinical trials. Both of the SARS-CoV and MERS-CoV outbreaks were largely controlled due to containment, patient isolation, and social distancing. Nonetheless, as the SARS-CoV-2 continues to spread farther than its predecessors, the need for a vaccine only becomes more urgent.

**Conclusions and perspectives**

The 2020 SARS-CoV-2 pandemic has sparked advancement in coronavirus research. Data from previous coronavirus outbreaks have been used to enhance the study of treatment and prevention measures for COVID-19. Studying the structure of the virus has allowed scientists to design testing processes rapidly, and new systems of testing are currently being designed to increase the speed and specificity of the process. The testing process is rapidly improving, yielding greater knowledge of who is or has been infected. These data could greatly advance regional decision-making concerning when to lift restrictions and deciding when individuals can resume their usual day-to-day activities.

Treatments for COVID-19 are also being rapidly developed to treat the symptoms of the disease, since no vaccine has currently been approved for mass distribution. Out of all the drugs tested, remdesivir has shown the most promising results. This drug has shown potential in low-powered studies, but hopefully, further research will shine light on its efficacy in the short term. Vaccine production is underway, and many types of vaccines are currently being researched and tested so that a vaccine can be available as soon as possible. There are many options for possible treatments of COVID-19, and, ultimately, it boils down to what is most effective, efficient, and available in the near future.

The combination of increased testing and efficient symptom treatment is an encouraging response to the pandemic. Currently, the spread of this virus shows promising decline, but these data will become more accurate as more people are tested and more time has passed. It is essential for governments to consider these factors before initiating the return to normal life.
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Conflict of interest

The authors declare no conflict of interest.

Author contributions

CLA, IM, RDPM, TMO, JP, KTLT, and HES reviewed the literature, wrote the manuscript, and revised the manuscript. CLA, IM, RDPM, TMO, JP, KTLT, and HES contributed equally to this manuscript. TPC carefully revised and cowrote the manuscript.

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