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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible coronavirus that emerged in late 2019 [1]. High SARS-CoV-2 transmissibility has led to a worldwide pandemic of acute respiratory disease, overwhelming health systems and causing many deaths. To date, this coronavirus is responsible for greater than 90 million cases in the United States and more than 1 million confirmed deaths [2].

As a coronavirus, SARS-CoV-2 belongs to a group of diverse viruses infecting many different animals including domesticated cattle and sheep, as well as avian mammals including bats [3]. New coronaviruses often lead to upper respiratory infections when they infect humans, infections that more recently have caused a wide clinical spectrum from mild-to-severe disease and death. Before the advent of these coronaviruses, these viruses were not thought to be pathogenic in humans, in fact, before 2002, most coronaviruses were believed to be quite mild and caused little or no disease in humans. SARS-CoV-2, a novel coronavirus responsible for COVID-19, is related to other pathogenic coronaviruses including SARS-CoV and MERS-CoV [3]. Although these other coronaviruses sparked a worldwide concern early due to rapid transmissibility and initial fatalities, both SARS-CoV and MERS-CoV were relatively quickly contained preventing a worldwide pandemic situation seen with SARS-CoV-2.

SARS-CoV-2 arose from Wuhan, China at the end of 2019 and, although attempts at containment were initiated, quickly spread to every country in the world [4]. The virus has proven to be highly contagious among humans, and with the timing of its emergence during the lunar New Year, travel of
families to and from Wuhan made containment logistically difficult [5]. SARS-CoV-2 has caused the largest viral pandemic in our lifetime and is a true threat to worldwide public health.

The emergence of SARS-CoV-2 in the United States, as in other countries, was met with great angst. The hospitals and health-care systems were quickly overwhelmed, and no treatments were known. People were dying and there was little that could be done other than supportive care. The SARS-CoV-2 pandemic highlighted the need for and importance of clinical trials to identify diagnostics, therapeutics, and vaccines that would combat this virus, as well as novel methods to get these therapies produced and trialed quickly but safely.

This review is written from the perspective of an anesthesiologist/clinical triallist who helped execute a plan at a large midwestern university to bring old and novel therapies for trial to help treat suffering people and to bring vaccines to trial with a goal of preventing severe disease and slowing viral transmission. To understand how and why this plan was needed, a firm understanding of the virus itself, as well as its impact on society are also very important.

**VIRAL EMERGENCE AND EFFECTS ON SOCIETY**

**Emergence**

Before 2002, coronaviruses were thought to not cause serious infections in humans. In fact, coronaviruses were better studied in mammals other than humans as human pathogenic coronaviruses were not seen. The emergence of SARS-CoV in a southern China animal market altered that theory. Pathogenic in humans, SARS-CoV caused respiratory illness in more than 8000 people and caused 774 deaths worldwide [6,7]. Still another coronavirus, MERS-CoV, emerged in 2012. This virus was responsible for Middle East respiratory syndrome and led to respiratory infections in approximately 2428 individuals and killing 838 [8]. SARS-CoV and MERS-CoV had bat origins before jumping to new mammalian hosts. SARS-CoV invaded the Himalayan civet. In the Middle East, MERS-CoV jumped to the dromedary camel in the Middle East. Both of these coronaviruses subsequently infected humans, with deadly consequences [9,10]. SARS-CoV-2 may have also originated in bats as bats have a similar coronavirus relative, a coronavirus known as RaTG13 [11]. SARS-CoV-2 and RaTG13 have similar S-proteins with about 98% amino acid sequence homology, only dramatically differing in the sequence of the S-gene coding for the spike protein [11]. Following initial SARS-CoV-2 cases that dated to December 8, 2019, in Wuhan, the World Health Organization (WHO) was notified of a pneumonia outbreak of unidentified cause by the Wuhan Municipal Health Organization [12]. By mid-January, 2020, Chinese scientists had identified the pathogen as a betacoronavirus with a single-stranded RNA genome. By January 12, 2020, the complete viral RNA genome sequence was made publicly available via the GI-SAID database [12,13]. On January 30, the WHO declared SARS-CoV-2 a public health emergency with international potential. Unable to contain the
virus in China, and with a large international travel population, the highly transmissible virus was determined to be a threat in all countries. According to Johns Hopkins University, by August, 2020, 216 countries and regions from all 6 continents had reported more than 20 million cases of SARS-CoV-2 (now called COVID-19), overwhelming local health resources and leading to high mortality [14].

COVID-19 IN THE COMMUNITY

COVID-19 has had a tremendous impact on all communities in the United States but a disproportionate effect on communities of color. The COVID-19 pandemic has highlighted several health inequities within our health system. For instance, non-Hispanic Black or African American people and Hispanic people are both more than twice as likely to be hospitalized due to COVID-19 than non-Hispanic white people [14,15]. Further, non-Hispanic Native Americans or Alaska Native people are 3.1 times more likely to be hospitalized due to COVID-19 than non-Hispanic white people. Racial and socioeconomic factors play a role in these inequities. These factors likely contribute to these inequities including, comorbid conditions, access to health care, location, and type of housing. Historically, Black, Hispanic, Native American, and Asian American people are at higher risk of developing comorbid conditions including diabetes mellitus, reactive airway disease, and hypertension. These comorbid conditions may predispose a person to developing severe disease from COVID-19 [15,16]. It is thought that type of work can also predispose a person to developing COVID-19 as having a job that is considered essential, which cannot be performed remotely, or involves public interaction, can increase one’s exposure to symptomatic and asymptomatic individuals and thus increase the risk of contracting COVID-19 [17]. People in racial and ethnic diversity groups might be more likely to live in multigenerational homes [18], crowded conditions, and densely populated urban areas. Living under the same roof or in groups can make the viral mitigating factor of social distancing difficult. Some diverse populations might also have higher rates of uninsured people causing disparities in health-care access [18]. Finally, stresses of racism itself can lead to early aging in diverse groups and could contribute to the development of severe disease from COVID-19 [19].

Within our communities, COVID-19 disproportionately affects people living in nursing homes. Often, this population has a high number of elderly, frail adults who are more likely to have a multitude of comorbid conditions [20]. An inability to properly social distance, a lack of adequate ventilation at the beginning of the pandemic, and the higher likelihood of this population having a multitude of chronic conditions all contributed to the waves of COVID-related deaths we saw in nursing homes at different times during the pandemic. Without question, the nursing home population suffered tremendous death counts because of swift transmission of COVID-19 within this environment and an inability to adequately institute viral mitigating methods, especially early in the pandemic.
COVID-19 and pregnancy
Although COVID-19 was deadly in the community, it was also thought that SARS-CoV-2 might also influence growing populations. Pregnant people infected with the SARS-CoV-2 could be asymptomatic or symptomatic. COVID-19 symptomatic pregnant people were found to be at increased risk for developing severe sequelae of COVID-19 compared with nonpregnant reproductive-aged women [21]. Most evidence suggested that pregnant women did not have different symptoms from the virus than nonpregnant individuals but if they developed severe disease, the clinical course was heightened and worsened [21]. Pregnant women symptomatic with COVID with severe disease were at increased risks for intensive care unit (ICU) admission, need for mechanical ventilation and ventilatory support, and death compared with nonpregnant women of the same age [21].

UNDERSTANDING THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2
Understanding how to best attack and mitigate this virus requires an understanding of the molecular makeup of this novel coronavirus. Further, an understanding of how the virus binds and invades host cells is imperative to finding neutralizing targets.

Viral makeup
Coronaviruses, in general, are spherical, enveloped viruses containing a helical symmetry nucleocapsid and a single-stranded RNA genome [22,23]. SARS-CoV-2 shares approximately 80% genome sequence identity with SARS-CoV [23]. Similar to other coronaviruses, the SARS-CoV-2 RNA genome contains 6 functional open reading frames. These ORFs are arranged in order from 5’ to 3’: replicase (ORF1a/ORF1b), spike (S), envelope (E), membrane (M), and nucleocapsid (N) [23]. Another 7 ORFs are scattered throughout the viral genome and likely code for accessory proteins. Although many of these genes are similar to counterparts in other coronaviruses [23], the S-gene, coding for the spike protein, diverges and has a very different sequence [24]. As with attempts at therapeutics to neutralize previous coronaviruses, the spike protein of SARS-CoV-2 has become the target for preventative and therapeutic options [25]. The S protein of SARS-CoV-2 is a class I fusion protein that protects its fusion domain. This protein keeps the binding domain hidden and inactive until the virus finds a host cell with an appropriate receptor, and targets that cell for infection [25]. The fusion protein is then enzymatically cleaved, revealing a hook-shaped structure that is necessary for viral binding and incorporation into the membrane of the target cell [26,27]. It is suspected that nucleotide polymorphisms and mutations within the spike protein alter viral transmissibility and virus–host cell interactions [26]. The speed and efficiency of these mutations is remarkable.

SARS-CoV-2 can rapidly mutate and alter its conformation in order to adapt to its current environment [28]. Mutations in the SARS-CoV-2 genome have
allowed for changes in disease severity, viral transmission, and host immunity evasion. As such, containment attempts of SARS-CoV-2 have involved worldwide population vaccination coverage and physical mitigation methods (social distancing, hand washing, mask wearing) to control the spread of the virus. History will be able to determine the extent to which these methods were able to control viral transmission.

**COVID-19 receptor**

In humans, SARS-CoV-2 enters cells using the same receptor as SARS-CoV, a receptor known as angiotensin-converting enzyme 2 (ACE2). ACE2 is a type I membrane glycoprotein responsible for the conversion of angiotensin II into angiotensin 1. This receptor is highly expressed in the lungs, nose, heart, intestine, and kidneys of humans [29]. The SARS-CoV-2 S-protein receptor binding domain (RBD), a 211 amino acid sequence, has been the target for neutralizing antibodies, both host and manufactured. By neutralizing the SARS-CoV-2 RBD, it is felt that one could effectively block the virus and prevent worsening of symptoms and progression of disease. Although similar to that of SARS-CoV, the RBD of SARS-CoV-2 functionally facilitates a much stronger interaction and tighter bond between itself and the host cell [29].

**SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 PATHOGENESIS**

There is a wide range of SARS-CoV-2 clinical pathologic conditions in humans, spanning from asymptomatic infection to mild symptoms to severe respiratory failure and death. Asymptomatic infections have been well-documented [30,31]. One review performed before the introduction of COVID-19 vaccination estimated that 33% of people with SARS-CoV-2 infection never develop symptoms [31]. Asymptomatic infections were a confounder early in the pandemic because it had been believed that only symptomatic individuals had viral loads high enough to transmit infection. This theory proved false, and as the pandemic thrived, asymptomatic spread of disease was a major contributor to community positivity rates [31].

The original COVID-19 and several subsequent variants would bind to airway epithelial cells via the ACE2 receptor in the upper respiratory tract. Replicating and releasing from the upper airway cells, SARS-CoV-2 migrated into the lower airways. Here, SARS-CoV-2 would enter lung alveolar epithelial cells [32]. The rapid replication of SARS-CoV-2 in the alveoli triggers a strong immune response that precipitates a cytokine storm syndrome, which ultimately leads to acute respiratory distress syndrome and respiratory failure, a principal cause of death in COVID-19 patients [32]. Although far from universal, older patients (aged >60 years) and those with serious preexisting diseases (particularly obesity, pulmonary complications, and diabetes) have demonstrated a greater risk of progressing to severe COVID-19 disease and death.

All ages and genders are susceptible to SARS-CoV-2 infection. The median age of COVID-19 infection is around 50 years, and clinical manifestations can
differ dramatically with age. To date, 78% of hospitalizations and approximately 75% of all deaths related to COVID have occurred in the older than 65 years demographic [33]. Older men with comorbidities tend to develop severe disease, whereas most young people and children have only mild symptoms (nonpneumonia or mild pneumonia), if they have any symptoms at all. When infected with COVID-19, the most common symptoms are fever, fatigue, and dry cough, with sputum production, headache, hemoptysis, diarrhea, anorexia, sore throat, chest pain, chills. Nausea and vomiting are somewhat less common symptoms [34]. In the age of delta and omicron, a sore throat and persistent cough have been commonly described [35]. Self-reported olfactory and taste disorders were also reported by patients in Italy, and subsequently described worldwide [36]. Viral incubation period was about 3 to 5 days because most people showed signs of viral infection on day 6 to 10 after exposure. Symptoms of dyspnea and pneumonia developed within a median time of 8 days from illness onset [37].

The degree of SARS-CoV-2 contagiousness may be due to certain virologic features of SARS-CoV-2. Human-to-human transmission can occur through respiratory droplets containing SARS-CoV-2 particles and can spread by speech, coughing, or sneezing [38]. The recipient mucous membranes of the eyes, nose, or mouth are viral portals. Additionally, transmission can occur by direct contact with contaminated surfaces because the virus is able to survive outside of the host for at least several hours [38–40]. Typically, respiratory viruses have the highest transmission rate from human to human while the infected person has viral symptoms. It is thought that the virus is at its peak during this time. COVID-19 is also thought to be most transmissible during the symptomatic period as well [41]. However, the possibility of viral transmission from an asymptomatic individual [42] exists as there is clear evidence of asymptomatic or presymptomatic spread of SARS-CoV-2 demonstrated by colonization and replication in a human throat during the initial infection [43,44]. In fact, it is possible that unknown and asymptomatic infections might account for approximately 80% of transmitted cases because of this high viral transmissibility during the asymptomatic period [42]. Asymptomatic period infectiousness, aerosolized particles, and viral survivability outside of the host likely contribute greatly to the rapid global spread of the virus. Public health mitigation interventions to reduce transmission have proven successful in China and several other countries, such as South Korea.

Severe acute respiratory syndrome coronavirus 2 diagnosis
The COVID-19 pandemic has highlighted the imperative nature of prompt and accurate viral diagnosis. Currently, polymerase chain reaction (PCR) genomic amplification methods represent the gold standard [45–48]. PCR testing, although accurate, is very expensive due to the complexity of the process and the required technical elements. Requirements for testing include PCR reaction reagents, expensive analysis machines, and experienced laboratory technicians [45]. Early in the pandemic, important supplies including
nasopharyngeal swabs used for sample collection were in short supply greatly limiting the ability to test symptomatic people adequately and efficiently. An inability to adequately test patients in the first days of the pandemic likely contributed to the rapid transmission of the virus as people could not be isolated and contact tracing was not possible. Further complicating the testing deficiencies in the United States, PCR reaction reagents were lacking, and supply did not meet demand. Eventually, as the supply of collection equipment and of PCR reagents production was increased, efficient testing was generally made widely available. Mass testing centers were set up throughout the country so that people could quickly be screened for COVID-19 if they had contact with a known COVID-19 patient or if they had symptoms of COVID-19.

PCR testing in developing countries has been particularly challenging. Economic disparities in developing and underdeveloped countries prevent effective mass PCR testing programs. As such, other methods are required to screen symptomatic people. Rapid antigen and antibody tests and immunoenzymatic serologic tests became inexpensive to produce and easy to use. Rapid testing has become the most widely used technique for monitoring the spread of SARS-CoV-2 infection. These low-cost point-of-care tests enabled for effective viral surveillance systems. Yet, in other countries where COVID-19 tests (either Rapid or PCR tests) were in short supply, other systems needed to be developed to screen patients. In the absence of diagnostic testing, it became necessary to consider the patient’s symptoms, contact history, and also the patient’s medical history. The integration of all of these elements provides a solid foundation for adequately diagnosing COVID-19 infection and effectively managing and containing the COVID-19 pandemic [49].

Accurate and early COVID-19 diagnosis is crucial for controlling its spread. Testing 36 to 72 hours following a known exposure is recommended, especially if one is symptomatic and is at high risk for becoming symptomatic. False-negative results can also arise when nasopharyngeal or oral swabs are improperly used by collection technicians, therefore multiple detection methods should be available to confirm a COVID-19 diagnosis. One such alternative method was chest computed tomography (CT). COVID-19 patients demonstrated typical CT features including bilateral multilobar ground-glass opacities with a peripheral or posterior distribution. Thus, it has been suggested that CT scanning combined with repeated swab tests should be used for individuals with high clinical suspicion of COVID-19 but are testing negative for the virus [50].

With an understanding of SARS-CoV-2 from a molecular and pathogenic standpoint, and diagnostics and mitigation methods in place, the next frontier to conquer was therapeutics. Patients hospitalized were being treated symptomatically, although no therapeutics had been developed to combat the virus. The collaboration of private and public sectors was brought together in an effort known as WARP SPEED. The goal of WARP SPEED was to have these sectors work together to rapidly develop and trial therapeutics.
OPERATION WARP SPEED
In response to the COVID-19 pandemic, the US government quickly activated Operation Warp Speed (OWS). OWS created a partnership between the Department of Health and Human Services and the Department of Defense (DOD) with the goal of accelerating the development of a COVID-19 vaccine [51]. This partnership decided the best strategy would be to use different private companies to use different vaccine platforms to generate expeditious delivery of safe and effective vaccines. These companies also took steps, such as starting large-scale manufacturing during clinical trials and combining clinical trial phases or running them concurrently. Clinical trials gathered data on safety and efficacy, with more participants in each successive phase (eg, phase 3 has more participants than phase 2) [51,52]. Common to each of these companies was the compressed timelines. To meet OWS timelines, some vaccine companies relied on data from other vaccines using the same platforms, where available, or conducted certain animal studies at the same time as clinical trials. However, as is done in a nonpandemic environment, all vaccine companies gathered initial safety and antibody response data with a small number of participants before proceeding into large-scale human studies (eg, phase 3 clinical trials) [51,52]. There was no compromise of safety and effectiveness in the development of these vaccines.

Anti-COVID-19 therapeutics
When COVID-19 first came to the United States, we were ill prepared to treat the disease. Since then, convalescent plasma, monoclonal antibodies, intravenous antivirals, and oral antivirals have become commonplace for early intervention. The only late intervention therapy that has proven useful once a person is mechanically ventilated is steroid use.

CHLOROQUINE AND HYDROXYCHLOROQUINE
Although not a WARP SPEED initiative, anecdotal evidence from around the world suggested a potential use for the drugs, chloroquine and hydroxychloroquine. These antimalarial and immune altering medicines were thought to elicit a therapeutic benefit by the inhibition of cellular entry by the virus [53]. These medicines are known to inhibit the glycosylation of cellular receptors and prevent, at least partially, virus–host receptor binding. Further, they can increase the endosomal pH to inhibit membrane fusion [54]. It is currently accepted that these medicines provide no clinical benefit to effectively treat patients with COVID-19 [54,55]. Even though some studies showed they can inhibit SARS-CoV-2 infection in vitro, clinically this has not proven to occur. Further, 2 clinical studies demonstrated no association with death rates in patients receiving chloroquine or hydroxychloroquine compared with those not receiving the drug [54]. On 15 June 2020, owing to the side effects observed in clinical trials, the US Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) for chloroquine and hydroxychloroquine as a treatment of COVID-19 [56].
PASSIVE IMMUNITY AND CONVALESCENT PLASMA

Without effective treatments available to combat COVID-19, a group of scientists and physicians looked to a historical therapy that had been used to treat previous viral disease including measles and Ebola. This therapy relied on having donors who had recovered from COVID-19 and were likely to have levels of neutralizing antibodies in their plasma. Collecting this plasma and transfusing it into a sick person would potentially provide therapeutic benefit to the sick patient [57].

Under the guidance of the Mayo Clinic Expanded Access Program, convalescent plasma could be collected and administered to hospitalized patients. The program was expanded to nearly 2900 hospitals in every state and several countries, and more than 70,000 patients were transfused 1 or 2 units of plasma. Although never designed to be a randomized clinical trial, the Mayo EAP became the largest trial testing the safety of convalescent plasma transfusions [58]. Several randomized controlled trials, including the large RECOVERY trial in the United Kingdom [59], failed to establish survival benefit to transfused patients versus controls. Others have pointed to trial deficiencies to explain the lack of effect. First, convalescent plasma was usually administered to patients when they had already developed severe disease while hospitalized. Second, plasma antibody titers were not adequately measured. More recently, high-titer convalescent plasma was used to treat outpatients with COVID-19 in a randomized controlled trial [60]. Using convalescent plasma in this manner reduced hospitalizations by 50%. As convalescent plasma will be readily available and inexpensive to collect in any area where a COVID-19 spike is occurring, the WHO should reevaluate its position and allow convalescent plasma to be used in countries where monoclonal antibodies are not in plentiful supply.

PASSIVE IMMUNITY AND MONOCLONAL ANTIBODIES

Arising from the work done with convalescent plasma, and with knowledge from past experiences with viruses including Ebola, monoclonal antibodies were developed as therapeutic options for the treatment and potential prophylaxis for COVID-19 [61]. Similar to convalescent plasma, monoclonal antibodies are a form of passive immunity where laboratory generated antibodies are targeted to specific epitopes on the virus. In the case of SARS-CoV-2, multiple antibodies were created to bind the viral spike protein to prevent viral binding and invasion of the host cell. In contrast with convalescent plasma, which consists of many antibodies contained in plasma, monoclonal antibodies are directed toward specific targets and selected specifically for their ability to neutralize the virus [24,62].

Bamlanivimab (Eli Lily) was the first monoclonal antibody given a EUA by the FDA in November 2020. This single monoclonal antibody was approved to treat mild COVID-19 disease in outpatients who were at risk of developing severe disease and being hospitalized. Specifically, Bamlanivimab (Bam) is a neutralizing human IgG1κ monoclonal antibody [63]. In a clinical trial known
as the BLAZE-1 trial in patients with mild-to-moderate COVID-19, this monoclonal antibody showed an effect of on reducing viral loads in treated patients versus untreated control patients. More important than the viral load reduction, however, was that the treated patients showed less emergency room visits and reduced hospitalizations compared with untreated control patients [64]. In the highest risk of developing severe disease group of patients (body mass index >35 or aged >65 years), there was a sharp contrast between the treated and untreated with treated patients showing pronounced reductions in emergency room visits and hospitalizations [64].

Unfortunately, because of the rapid rate in which SARS-CoV-2 can mutate its spike protein, this monoclonal antibody became less effective as variants began to circulate. The large number of COVID-19 variants developed resistance to bamlanivimab neutralization. This led the FDA and CDC to revoke the EUA for this monoclonal antibody because it was no longer useful in the treatment against COVID-19 variants beta and gamma [65]. Bamlanivimab did demonstrate effectiveness against the Delta variant when combined with a second monoclonal (Etesevimab) and its use was briefly resumed but stopped again because it had little efficacy versus the Omicron variant [63].

A second authorized monoclonal therapeutic consisted of the 2 monoclonal antibodies casirivimab and imdevimab and was developed by Regeneron. Similar to the Lily monoclonal, this novel monoclonal antibody cocktail had directed activity versus the SARS-CoV-2 spike protein and was distributed under the name REGEN-COV. This cocktail was trialed as both an infusion and a subcutaneous injection [66]. In November, 2020, the FDA issued an EUA for REGN-COV to be used in at risk patients with COVID-19 who currently had mild-to-moderate symptoms. In clinical trials, more than 4000 outpatients with mild-to-moderate COVID-19 and at least one risk factor for severe disease were randomized to receive either REGN-COV or placebo [67]. The REGN-COV treatment groups showed sharp reductions in COVID-19–related hospitalization or all-cause death, and a more rapid resolution of COVID-19 symptoms compared with placebo. The EUA was then amended to include its use as a postexposure prophylactic treatment because treated individuals demonstrated a profound decrease in developing symptomatic COVID-19 compared with untreated controls in clinical trial. In a postexposure prophylaxis arm of the clinical trial, 1505 participants who lived in a household with a patient infected with COVID-19 but were asymptomatic and had a negative SARS-CoV-2 test. The treatment group demonstrated an 81% risk reduction in the development of PCR-confirmed COVID-19 infection through 29 days [68]. This would be particularly important for nursing home patients, and others who live in close quarters with a person infected with COVID-19, as well as for COVOD-19 negative immunocompromised people with a strong exposure to COVID.

Similar to the Lily monoclonal antibody, REGEN-COV proved less effective against increasing COVID-19 variants, and the EUA was eventually withdrawn for this treatment. Other monoclonal antibodies have been granted
EUA by the FDA for use against various COVID-19 variants. One such monoclonal, sotrovimab was created from an antibody identified in 2003 in a survivor of SARS [69]. This monoclonal, developed by Glaxo Smith Kline, showed initial effectiveness against Delta and Omicron variants in the COMET-ICE clinical trial. This trial, similar to others, demonstrated effectiveness in outpatients with COVID-19 experiencing mild-to-moderate symptoms but who were at risk of developing severe disease. Ultimately, the SARS-CoV-2 variants evaded this monoclonal, and the EUA was withdrawn. Finally, Astra Zeneca has developed a 2 monoclonal antibody cocktail called Evusheld that is being trialed as a prophylaxis drug for immune compromised patients who are either resistant to a COVID-19 vaccine, or unable to mount a robust antibody response to the vaccine. It is thought that this passive immunity can provide up to 6 months of protection against developing symptomatic COVID-19 [70].

**DEXAMETHASONE**

Treatments for patients with severe disease from COVID-19 requiring high flow oxygen or mechanical ventilation have been a challenge. Neither convalescent plasma nor monoclonal antibodies demonstrated any survival benefit to patients with this late-stage COVID-19. Further, neither treatment demonstrated a reduction in days on the ventilator or days hospitalized once the virus had caused severe disease. With treatments limited, physicians looked to dexamethasone, a corticosteroid that suppresses the immune response. It was felt that by suppressing the cytokine storm, dexamethasone could provide benefit [71]. A large clinical trial known as the RECOVERY trial in the United Kingdom demonstrated that when patients with severe COVID-19 were treated with dexamethasone (6 mg once daily for up to 10 days), they saw a reduction in 28-day mortality. No benefit was observed in patients not requiring oxygen. This trial changed clinical practice, which had dictated that corticosteroids were contraindicated and rewrote the clinical treatment guidelines so that COVID-19 patients requiring supplemental oxygen could be administered dexamethasone [72].

**Antivirals**

Until recently, remdesivir had been the only antiviral medicine approved by the FDA to be used in COVID-19 patients. Two large randomized clinical trials have been performed using remdesivir, a study carried out by the VA and the ACTT-1 trial. The ACTT-1 trial found that IV remdesivir provided no survival benefit but patients who recovered from COVID-19 were able to be discharged earlier from the hospital [73]. The VA study also showed no survival benefit but demonstrated that patients stayed in the hospital longer than untreated patients. It has been speculated that the VA study did not follow the same protocol as the ACTT-1 trial, specifically that patients stayed in the hospital for the full length of their remdesivir course [74]. In ACTT-1, patients were discharged from the trial when they met the trial endpoint, no further
infusions were administered. This detail may have not been properly communicated and could explain the longer hospital stays observed in the VA trial.

An oral antiviral medicine known as Paxlovid has just come to market. This oral pill is administered to a person with very early COVID-19 twice per day for 5 days. Paxlovid has many medication interactions with other medicines, so its use is limited to people with no contraindications [74]. The clinical trial investigating Paxlovid in outpatients with risk factors for developing severe disease, demonstrated a marked reduction in hospitalizations (70%) compared with untreated control patients, and no deaths. More recently, several patients have found themselves with rebound COVID-19 infections following their 5-day course of Paxlovid. This is a phenomenon that requires further study [75,76].

**ACTIVE IMMUNITY AND VACCINES**

As soon as COVID-19 was declared a public health emergency and classified as a pandemic, an intense worldwide effort was undertaken to develop safe and effective COVID-19 vaccines. Vaccines generated were from several different "classes"; however, their general principle was all the same—to force the human immune system to generate anti-COVID antibodies in the absence of active infection. The antibodies, then, would serve to survey and protect a person should they contract the virus. The development of the vaccines had to be expeditious, and the clinical trials had to be incredibly efficient in order to deliver these too naive populations within a finite timeline.

**MESSENGER RNA VACCINES**

Scientists have developed a new type of vaccine that uses a genetic molecule called messenger RNA (mRNA) that codes for a portion of the virus rather than a part of an actual bacteria or virus. These novel vaccines had been developed for other viruses but had never been manufactured on a large scale. Their premise is to use mRNA, a genetic molecule necessary for protein production. In essence, these vaccines are delivering a genetic blueprint to human cells to make a protein designated by the mRNA and then the body develops antibodies against the produced protein. Once cells finish making a protein, the mRNA quickly breaks down by cellular enzymes. mRNA from vaccines does not enter a cell’s nucleus and does not alter native DNA.

**PFIZER VACCINE**

This mRNA vaccine was the first COVID-19 vaccine to receive EUA. Similar to other mRNA vaccines, it has an mRNA message to build the spike protein. This mRNA is enclosed within a lipid envelope. A US clinical trial involving 43,548 participants, funded by BioNTech and Pfizer, demonstrated that this vaccine (2 doses, 3 weeks apart) was very effective in preventing symptomatic COVID-19. In fact, 95% of individuals administered the vaccine did not contract COVID-19 [77]. A clinical trial was also performed in Israel with 1.2 million people and the efficacy of the vaccine was confirmed [78]. Side effects were minimal, usually consisting of fatigue, arm soreness, headache, and/or
fever. A rare but significant side effect following vaccination can include myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) [79]. These side effects are more likely following the second dose of the vaccine and occur more commonly in teenage boys. As immunity begins to wane somewhere around 5 to 6 months after dose 2, it is recommended that a third shot be administered as a booster dose. This has shown in studies to restore immunity back to the high efficacy level seen after the second shot. Especially in people with compromised immune systems, a fourth shot is recommended as a second booster as well.

More recently, the Pfizer mRNA vaccine has been approved for children aged 5 to 11 years. The side effect profile is like that in adults, although the incidence of myocarditis seems much lower. Overall efficacy is similar to what is seen in adults, despite the dose being approximately one-third the dose that the adult receives. Again, waning immunity after 5 to 6 months has prompted to recommendation to issue a booster shot at that time [80].

MODERNA MESSENGER RNA VACCINE
The second COVID-19 vaccine to be granted EUA by the FDA and CDC also used an mRNA platform and came from Moderna. Although it has a very similar makeup to the Pfizer vaccine, they differ in the amount of mRNA (30 mcg Pfizer vs 100 mcg Moderna) and the lipid envelope is manufactured using slightly different lipids. In a US clinical phase 2/3 trial involving more than 30,000 individuals, only 11 developed symptomatic COVID-19 following 2 doses 1 month apart [81]. The vaccine had a 94% efficacy rate and was 100% effective against severe illness, hospitalization, and death from COVID-19 [81]. The trial population included more than 7000 people aged older than 65 years, and another 5000 who were aged 65 years or younger but had comorbidities that placed them in a group most at risk of developing severe COVID-19. Paramount to the success of these clinical trials to be completed in the contracted timeline was the need to ensure that all ages, genders, and diversity of communities were appropriately represented and reflected the US population. Although the Moderna was thought to have longer lasting immunity compared with the Pfizer vaccine, antibody levels did begin to wane after approximately 6 months and a booster was recommended.

The Moderna vaccine clinical trial for children, aged 11 to 17 years had been completed in the United States but no EUA was initially authorized because of concerns of myocarditis and pericarditis, in especially teenage boys. Data has now been collected worldwide and Moderna was deemed safe and effective in a unanimous vote by the FDA advisory committee on June 14, 2020. Overall, the incidence of myocarditis in this age group is very rare but a warning has been attached to the vaccine label listing this as a potential adverse effect, especially after the second shot [79].

JOHNSON AND JOHNSON ADENOVIRAL VACCINE
The J&J/Janssen COVID-19 vaccine contains a piece of a modified SARS-CoV-2 viral DNA coding for the COVID-19 spike protein. The vector adenovirus,
which typically causes the common cold, has been modified so that it cannot reproduce itself and thus is nonpathogenic. This adenovirus vector serves as a shuttle to move the spike protein DNA into cells where the cells then use their own machinery to synthesize the spikes [82]. The body then generates antibodies to these spike proteins to produce both acute and lasting immune responses to deter symptomatic COVID-19. The Johnson and Johnson vaccine had a lower efficacy rate for preventing symptomatic COVID-19 when compared with the mRNA vaccines (74%–78%) but this was billed as a one shot vaccine [82]. Real life data from this vaccine uncovered a rare but significant side effect where people developed blood clots with diminished platelet counts, and the FDA has now limited its use in favor of the mRNA vaccines. Further waning immunity after 5 to 6 months suggested the need for a booster to restore immunity levels, and the FDA and CDC issued a statement that receiving an mRNA booster would be recommended.

SUMMARY

Although there is plenty of room for criticism around the response by the United States to the COVID-19 pandemic, much was accomplished in a relatively short period of time. Beginning with the genomic sequence published by the Chinese before COVID-19 invading every country on earth, the United States had already begun to understand and characterize the pathogen. In relatively quick fashion, the response included an understanding of the virus itself, the development of testing to be able to provide early and efficient viral diagnoses, the development of effective treatments to help prevent people from dying from severe COVID-19, the development of treatments to help prevent disease progression and hospitalizations, the development of treatments to act as prophylaxis agents in close contacts, and finally the development of safe and effective vaccines to provide the world population immunity to protect them from severe disease, hospitalization, and death from COVID-19. The study continues, however, as evolving COVID-19 variants continue to find ways to evade immunity. Potential areas for future research include the development of newer vaccines with variant mRNA “blueprints” to better fight off infection and newer treatments, both antiviral medications and monoclonal antibodies to continue to treat people sick from COVID-19. Highlighted in this plan and in the future directions is the need to continue to be able to perform large and efficient clinical trials accurately representing the population of the United States, so that we can build the best treatments, build the best preventatives, and develop the best vaccines to keep all people, young and old, safe, and virus-free.

Disclosure

The author has nothing to disclose.

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