Management of Coronavirus Disease 2019 (COVID-19) Pandemic: From Diagnosis to Treatment Strategies

Zhina Hadisi, Tavia Walsh, Seyed Mohammad Hossein Dabiri, Amir Seyfoori, David Hamdi, Bahram Mirani, Erik Pagan, Armando Jardim, and Mohsen Akbari*

Following the emergence of severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012, the world is now combating a third large-scale outbreak caused by a coronavirus, the coronavirus disease 2019 (COVID-19). After the rapid spread of SARS-coronavirus (CoV)-2 (the virus causing COVID-19) from its origin in China, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020. From the beginning of the COVID-19 pandemic, a significant number of studies have been conducted to better understand the biology and pathogenesis of the novel coronavirus, and to aid in developing effective treatment regimens, therapeutics, and vaccines. This review focuses on the recent advancements in the rapidly evolving areas of clinical care and management of COVID-19. The emerging strategies for the diagnosis and treatment of this disease are explored, and the development of effective vaccines is reviewed.

Z. Hadisi, T. Walsh, Dr. S. M. H. Dabiri, Dr. A. Seyfoori, D. Hamdi,
E. Pagan, Dr. A. Jardim, Dr. M. Akbari
Laboratory for Innovation in Microengineering (LiME), Department of
Mechanical Engineering, Center for Biomedical Research
University of Victoria
3800 Finnerty Rd., Victoria, BC V8P 2C5, Canada
E-mail: makbari@uvic.ca

B. Mirani
Department of Mechanical and Industrial Engineering
University of Toronto
Toronto ON M5S 3G8, Canada

B. Mirani
Institute of Biomaterials and Biomedical Engineering (IBBME)
University of Toronto
Toronto ON M5S 3G9, Canada

B. Mirani
Institute of Biomedical Engineering (BME)
Ted Rogers Centre for Heart Research
University of Toronto
Toronto ON M5G 1M1, Canada

Dr. M. Akbari
Center for Biomedical Research
University of Victoria
3800 Finnerty Rd. Victoria, BC V8P 2C5, Canada

Dr. M. Akbari
Centre for Advanced Materials and Related Technology (CAMTEC)
University of Victoria
3800 Finnerty Rd. Victoria, BC V8P 2C5, Canada

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adtp.202000173

DOI: 10.1002/adtp.202000173

1. Introduction

Since the first identification of human cases with symptom onset in December 2019 in Wuhan, China, severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 has spread rapidly across the globe, infected more than 30 million people in 212 countries and territories, and caused 950 000 deaths as of September 2020.[1–3] The coronavirus disease 2019 (COVID-19) has created an onerous burden on the global health care system and has led to an unprecedented increase in demand for intensive care units (ICUs).[4–6] In addition to the clinical implications and public health concerns, the COVID-19 pandemic has greatly affected the social fabric of nations and has caused severe global macroeconomic impacts.[7–9] SARS-CoV-2 is the seventh species of coronavirus that is pathogenic to humans and transmittable between people.[10,11] Among these coronaviruses, SARS-CoV, SARS-CoV-2, and the Middle East respiratory syndrome (MERS)-CoV can cause severe disease and fatality, while HKU1 (discovered in 2005), NL63 (discovered in 2004), and OC43 and 229E (both characterized in the 1960s) are known to produce mild clinical symptoms.[12] While SARS-CoV-2 mainly attacks the lower respiratory system causing viral pneumonia, emerging data suggests that it may also damage the heart, gastrointestinal system, liver, kidney, and central nervous system, resulting in multiple organ failure.[13–17] Similar to other coronaviruses, SARS-CoV-2 contains a single-strand positive-sense ≈30 kb RNA genome that is encapsulated within a membrane envelope.[3,18,19] This genome is ≈80% and 50% identical to SARS-CoV and MERS-CoV, respectively; however, more than 90% of the sequence is shared with some of the coronaviruses isolated from bats and pangolins, suggesting a zoonotic origin for COVID-19.[3,20,21]

The containment of the novel coronavirus relies in part on effective diagnosis and active symptom monitoring. Real-time reverse transcription polymerase chain reaction (RT-PCR) has been the primary technique, due to its high specificity, for diagnosing COVID-19 through the amplification of specific regions of the SARS-CoV-2 genome.[11,22] High-throughput sequencing approaches, though capable of generating whole viral genomes that are critical for molecular epidemiological tracking of SARS-CoV-2, have a slow turnaround time and are not commonly used for diagnosis in other cases.[23] Based on patient symptomology, computed tomography (CT) imaging of the chest and lungs

Table 1. Differences between COVID-19, SARS, and MERS viruses.

Respiratory infections	Common symptoms (% of cases)	Less common symptoms	Emergence	Incubation period	Transmission	Receptor	Cell line susceptibility	Receptor distribution
COVID-19	• Fever (81–91) • Cough (48–68) • Dyspnoea (19–31) • Sore throat (29) • Dizziness/confusion (22) • Smell/taste dysfunctions (28–41) • Diarrhea (16) • Nausea/vomiting (6)[86]	• Nasal congestion • Headache • Muscle aches • Chills[87]	Wuhan, China, potentially related to a food market (December 12, 2019).[88]	≈14 days[89]	• Confirmed between humans (respiratory droplets) • Postulated contaminated dry surfaces (self-inoculation of nose, eyes, or mouth mucous membranes)[90]	ACE2	• Respiratory tract • Goblet cells in the nose • Intestinal tract • Kidney • Liver[91]	• Alveolar monocytes, macrophages • Liver with inflammatory cell infiltration • Heart • Small intestine • Respiratory tract epithelium[92]
MERS	• Fever (81.7–98) • Cough (56.9–83) • Dyspnoea (22–72) • Sore throat (9.1–14) • Dizziness/confusion (5.4) • Diarrhea (19.4–26) • Nausea/vomiting (14–21)[86]	N/A	Identified from the saliva of a patient with acute pneumonia and renal failure in Jeddah, Saudi Arabia, 2012.[93]	2–14 days[48]	• Close person-to-person contact (respiratory secretions from coughing and sneezing) • Close contact with infected dromedary camels[94]	DPP4	• Respiratory tract • Intestinal tract • Genitourinary tract • Liver • Kidney • Neurons[95]	• Respiratory tract epithelium • Kidney • Small intestine • Liver and prostate • Activated leukocytes[95]
SARS	• Fever (99–100) • Cough (57–75) • Dyspnoea (40–42) • Sore throat (13–25) • Dizziness/confusion (40–43) • Diarrhoea (23–70) • Nausea/vomiting (20–35)[86]	• Intestinal symptoms[96]	Animal host transmission to humans in animal markets, Guangdong province, China, November 2002[97].	2–12 days[98]	• Close person-to-person contact (respiratory droplets)[99]	ACE2	• Respiratory tract • Kidney • Liver[95]	• Arterial, venous endothelium • Arterial smooth muscle • Small intestine • Respiratory tract epithelium • Liver with inflammatory cell infiltration • Alveolar monocytes, macrophages[95]

has been used as an auxiliary diagnostic method[24,25]; however, this technique does not distinguish between various other viral pneumonia.[24,26] Alternatively, serological test kits that detect specific viral antigens or antibodies against SARS-CoV-2 using enzyme-linked immunosorbent assay (ELISA) are being developed or are under clinical evaluation.[27–29] Overall, the immediate response to the COVID-19 pandemic urgently requires high-throughput diagnostic tests with increased sensitivity, high specificity, reduced cost, and rapid turnaround times.

In addition to diagnostics for detecting SARS-CoV-2, major global campaigns have been mounted to better understand the pathophysiology of the disease, develop optimized clinical approaches for managing symptoms, and identify strategies for developing effective therapeutics and vaccines. One approach to treating patients with advanced symptoms has relied on repurposed drugs known to be effective against other RNA viruses as potential treatments for COVID-19.[30] In particular, antiviral drugs such as lopinavir, remdesivir, arbidol, baricitinib, and chloroquine (CQ), agents postulated to disrupt viral replication and maturation, have been enrolled in clinical trials to assess their therapeutic effects against SARS-CoV-2.[31–34] Additionally, due to the relatively large basic reproduction rate (basic reproduc-

tion number of ≈3) of the virus, the development of vaccines appears essential for controlling the spread of SARS-CoV-2.[35] Pre-existing vaccines with potential effects against SARS and MERS coronaviruses can facilitate the development of vaccines against SARS-CoV-2, given the significant sequence homology between the viruses.[30] In this review, we summarize the known biological characteristics of SARS-CoV-2 and highlight the differences with SARS-CoV and MERS-CoV. The established and emerging diagnostics and treatment options for COVID-19 are reviewed, and the ongoing research on the development of vaccines against COVID-19 is explored.

2. Coronavirus and Respiratory Diseases

The respiratory illnesses caused by coronavirus (SARS-CoV and MERS-CoV) are highlighted and comparable to COVID-19. This section will discuss the current knowledge on etiology, epidemiology, clinical presentation, and histopathological features of these pathogens. **Table 1** summarizes the main differences between SARS-CoV, SARS-CoV-2, and MERS-CoV coronavirus diseases in terms of symptoms, emergence, incubation period, transmission, and biological characteristics.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

2.1. SARS

SARS-CoV is a member of the Coronavirus genus in the *Coronaviridae* family and is characterized by the presence of a large positive-sense RNA genome (27.9 kb).[36] The outbreak of SARS was initially identified in Foshan, China, in November 2002 and emerged in mainland China by February 2003. The outbreak spread to North America and Europe (encompassing 29 countries) by infected international travelers. SARS was contained by July 2003 with 8096 reported cases and 774 deaths during the outbreak period.[37–39] However, confirmed cases were reported in Singapore, Taiwan, and China from September 2003 to May 2004, and mainly traceable to laboratories working with SARS.[40] No new suspected cases have been reported since May 2004. Genomic analysis indicated that SARS-CoV spread from a bat to another host, likely a palm civet (*Paguma larvata*), and was transmitted to humans in live exotic animal markets (**Figure 1**).[41] This was consistent with the later discovery of a colony of horseshoe bats in China with genetically similar coronaviruses.[41]

SARS-CoV is mainly transmitted through close person-to-person contact and the exchange of respiratory droplets formed through coughing or sneezing, or by touching contaminated surfaces.[42,43] Infection symptoms manifest 2–12 days following infection and include a high fever (>38 °C), myalgia, malaise, headache, body aches, diarrhea (10–20%), and a dry cough that may lead to hypoxia. Moreover, infected individuals present with low lymphocyte and blood platelet counts and elevated levels of C-reactive protein and lactate dehydrogenase.[37] Elderly and immunosuppressed patients were the most vulnerable to SARS-CoV and accounted for a disproportionate number of fatalities.[37,44]

SARS-CoV primarily targeted the immune system, causing low levels of lymphocytes and epithelial cells of the respiratory tract, which resulted in diffuse alveolar damage.[45] The histopathology was dependent on the duration of illness and varied for the different stages of the disease. Acute diffuse alveolar damage occurred in the primary stage, followed by the appearance of acute fibrinous and pneumonia in subsequent phases.[46] Bradley and Bryan reported a pathologic result obtained from an open lung biopsy of a patient with early phase SARS-CoV (one week after symptom presentation).[37] This revealed a mild increase in interstitial lymphocytes and alveolar macrophages with hyaline membrane formation. The autopsy of the lung tissues revealed bronchial epithelial denudation, loss of cilia, and squamous metaplasia morphological changes. A noticeable increase in macrophage density in the alveoli and the interstitium was also reported. Cytomegaly, characterized by nuclear enlargement and amphophilic granular cytoplasm, was present in the alveolar pneumocytes, and viral particles were found in dilated secretory vesicles in the cytoplasm of epithelial cells. Furthermore, significant atrophy of the white pulp of the spleen was detected in one patient.[47]

2.2. MERS

MERS is a viral respiratory disease caused by the coronavirus MERS-CoV, which emerged in 2012, 10 years after the outbreak of SARS-CoV.[48] MERS-CoV is the sixth discovered coronavirus that has a long positive-sense RNA genome (30.1 kb).[49] The single-strand SARS-CoV and MERS-CoV genome is translated into two large polyproteins called pp1a and pp1b. The pp1a and pp1b polyproteins are cleaved into 16 nonstructural proteins (nsps) to conduct the replicase-transcriptase of the virus. The envelope spike glycoprotein of SARS-CoV and MERS-CoV bind to the cell-surface receptors angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP-4), respectively. The viral RNA genome is released into the host cell's cytoplasm following membrane fusion and the subsequent translation of polyproteins, cleaved into 16 nsps by proteases, and concludes with viral genome replication.[44,50]

The first case of MERS was reported in Saudi Arabia, where MERS-CoV was discovered in the sputum of a deceased patient with acute pneumonia and subsequent renal failure.[48] MERS-CoV was then spread from the Arabian Peninsula by infected international travelers and resulted in person-to-person nosocomial transmission (Figure 1). As of January 2020, MERS-CoV cases were reported in 27 countries with 2519 confirmed cases and 866 fatalities.[51] Since bats are known reservoirs of different types of coronavirus, initial studies focused on bats as the reservoir of MERS-CoV.[52] This hypothesis was initially supported by a study in which fragments of the MERS-CoV genome was found in a bat colony, similar to the human isolated virus.[53] However, later serological and genetic studies found neutralizing antibodies and MERS-CoV RNA in dromedary camels, suggesting that camels were the intermediate hosts or reservoirs of MERS-CoV, and transmitted the virus to humans.[54,55]

Nosocomial transmission has been reported as the most common route of human-to-human infection transmission.[56] For instance, in May 2015, the outbreak of MERS in South Korea occurred after the hospital admission of a single infected individual returning from the Middle East. The transmission from this patient caused MERS outbreaks in 16 hospitals, resulting in 186 cases and 36 reported deaths (19.4% fatality rate). The majority of patients were infected by this superspreader as MERS is capable of surviving on hard surfaces for several days; therefore, transmission occurred via touching infected surfaces in these health care facilities.[50] Fast transmission of MERS-CoV within households was also reported, as family members are in close contact and were easily exposed to the respiratory secretions of infected individuals.[57]

The elderly and people with chronic diseases of the heart, lung, and kidney, diabetes, and cancer are more susceptible to MERS due to the increased likelihood of progression to respiratory failure in such patients. MERS can be symptomatic or asymptomatic, however, higher fatality rates are observed in symptomatic patients, as the onset of symptoms appears when substantial virus shedding occurs within the body.[50] Clinical symptoms appear after an incubation period of 2–14 days, and are commonly fever, cough, shortness of breath, myalgia, sore throat, and headache. Patients diagnosed with MERS also present with abnormal chest X-rays, which show multilobar airspace disease, ground-glass opacities, and occasional pleural effusions.[58–60] Less commonly reported symptoms include diarrhea, nausea, vomiting (up to 33%), acute kidney injury (up to 50%), and neurological sequelae.[61] Leukopenia and lymphopenia were reported as the most common hemostatic laboratory derangements, while thrombocytopenia and anemia were present in some patients.[50]
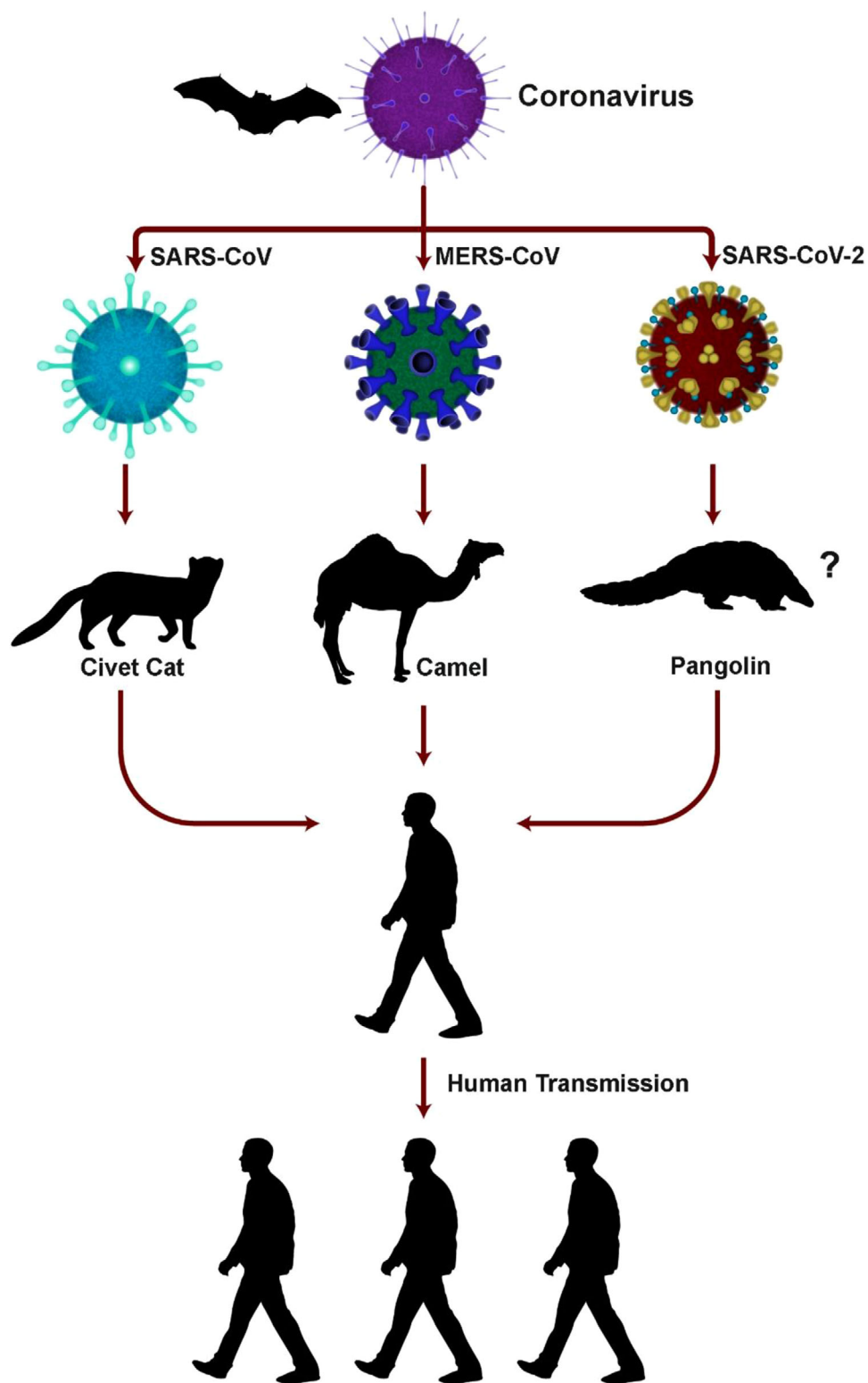
Figure 1. Schematic illustrating the transmission of SARS, MERS, and COVID-19 coronaviruses. Pangolins have been suggested as the intermediate carriers, however, the real source is still unknown, according to WHO.[66]

Furthermore, increased levels of aminotransferase were prevalent among patient with severe conditions.

Histopathological features of MERS-CoV have not been reported upon in depth, owing to the limited number of autopsy cases performed on patients infected with the virus. Ng et al. observed lung damage with exudative diffuse alveolar damage with hyaline membrane, deposition of alveolar fibrin, type 2 pneumocyte hyperplasia, and multinucleate syncytial cells in a patient who died 8 days after hospital admission.[62] Immuno-histochemistry analysis also confirmed the infection of pneumocytes (multinucleated epithelial cells) with MERS-CoV. These cells expressed DPP-4 surface antigens, which are the cell receptor of MERS-CoV. Furthermore, 50–150 nm spherical MERS-CoV particles were detected in the encased hyaline membrane and membrane-bound vesicles. Histopathological analysis of the brain, heart, lung, liver, kidney, and skeletal muscle tissues in a patient with T cell lymphoma showed acute kidney injury, portal and lobular hepatitis, and myositis with muscle atrophic changes, in addition to the necrotizing pneumonia. Additionally, accumulation of viral particles was observed in the respiratory epithelium and renal proximal tubular epithelial cells.[63] Histopathologic evaluations performed on the biopsy of the kidney tissue of a MERS-survivor revealed acute tubular necrosis and acute tubulointerstitial nephritis.[64] Based on human ex vivo and in vitro experiments, Yeung et al. suggested that the high incidence of MERS-induced renal failure was due to the hyperexpression of MERS against decapentaplegic homolog 7 (Smad7) and fibroblast growth factor 2 (FGF2) in kidney tissues.[65]

2.3. SARS-CoV-2

SARS-CoV-2 first emerged in Wuhan, China, and rapidly spread on an international scale. SARS-CoV-2 is one of the most aggressive forms of coronavirus, having infected ≈30 million people and having caused over 950 000 deaths, worldwide.[1–3,67] Symptoms typically associated with COVID-19 include tussis, fever or chills, and shortness of breath.[68] The prevalence of pre-existing medical conditions such as hypertension, obesity, diabetes, asthma, and cardiovascular disease are confounding factors linked to COVID-19 fatalities.[68]

SARS-CoV-2 has a bat origin and is transmitted to humans through an intermediate host, potentially pangolins.[10,19,69] SARS-CoV-2 shares 96% genomic sequence identity with the bat coronavirus RaTG13, and 79% and 50% sequence identity with SARS-CoV and MERS-CoV, respectively.[10] Viral strains detected in pangolins have a similar spike protein amino acid sequence as SARS-CoV-2, which binds to the human ACE2 receptor,[10,19,69] leading to the theory of pangolins as an intermediate species.

ACE2 is a cell membrane protein expressed in multiple organs throughout the human body. The primary role of ACE2 is in the renin-angiotensin system that serves to counterbalance the function of ACE by converting the vasoconstrictor Angiotensin 2 to Angiotensin-(1-7), essentially regulating blood pressure.[70,71] ACE2 has been shown to be the major cell receptor for SARS-CoV and SARS-CoV-2.[3,72] It has been suggested that patients suffering from hypertension and type 1 and type 2 diabetes have a higher risk of developing acute COVID-19,[26] due to the up-regulation of ACE2 by ACE inhibitors and Angiotensin type 2 receptor blockers.[26,73,74] The structure of SARS-CoV-2 is shown in **Figure 2**; displayed in yellow are the spike glycoproteins that SARS-CoV-2 uses to bind the ACE2 enzyme.
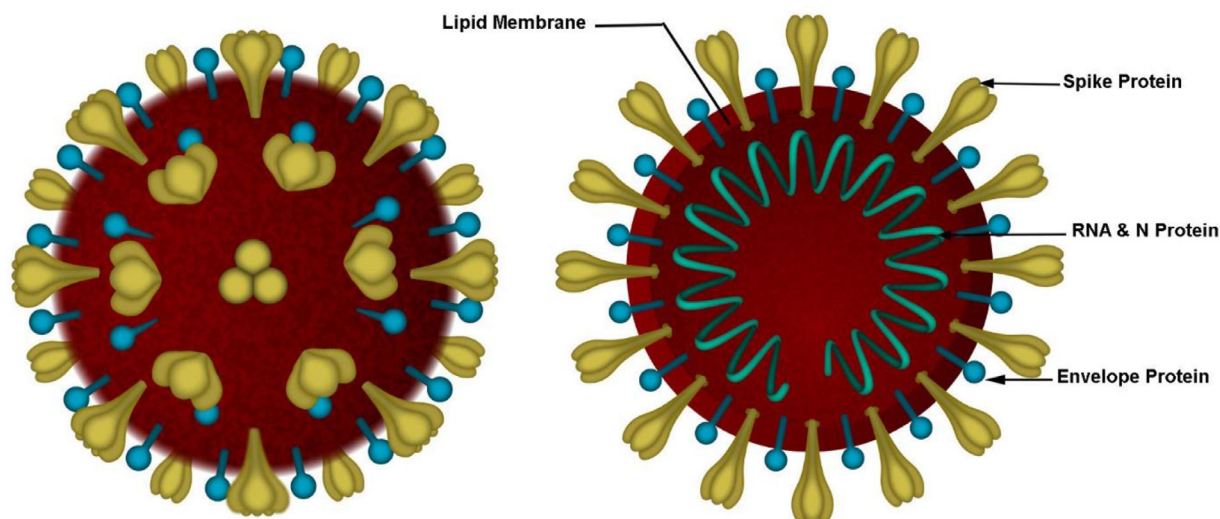
The prevalence of ACE2 in the lower respiratory tract[75,76] has been theorized as the reason for the lack of upper respiratory tract infections and symptoms.[14] Patient age is a factor that influences the severity of SARS-CoV-2 infections. Data from the USA Center for Disease Control show that hospitalization rates were highest among people more than 65 years old (13.8 per 100 000), while the hospitalizations of other age populations was lower than 6 per 100 000.[68] Data from the British Columbia Center for Disease Control in Canada show a similar trend with 67% of hospitalizations, 71% of intensive care visits, and 98% of fatalities occurring in patients >60 years old.[76]

Other important epidemiological aspects of the disease include the incubation period, transmission rate, infectious period, and pathogenesis. Lauer et al. found that the median incubation period was 5.1 days and that 97.5% of infected patients displayed symptoms within 11.5 days.[77] Several studies found similar incubation periods for SARS-CoV-2.[35,78,79] The transmission rate of SARS-CoV-2 has been estimated by multiple sources to be 2.2.[35,80,81] The infectious period for those afflicted with the SARS-CoV-2 virus is still being debated, however, He et al. developed a model showing that infectiousness begins 2–3 days prior to the development of symptoms and diminishes after a week with symptoms.[82] A brief case study by Zou et al. confirmed infection by asymptomatic patients[83] while another case study by Rothe et al. has identified viral transmission while the patient was in the incubation period.[84] The evidence points to increased transmissibility of the virus in the early stages of infection.

Once infection has taken place, the COVID-19 disease progresses with the initial common symptoms of fever, cough, fatigue, and muscle aches.[14] Symptoms then progress to shortness of breath and difficulty breathing, before developing into acute pneumonia.[14] Chest CT scans showed ground glass opacities in the lungs that became worse as the disease progressed.[85] Lastly, cardiovascular injury was observed in some patients, while elevated cytokine levels (including some proinflammatory cytokines) were detected in the patient's blood.[14]

3. Diagnostic Tests

Patients with COVID-19 pneumonia possess nonspecific symptoms such as cough, fatigue, and shortness of breath, which cannot be considered for an accurate diagnosis as these symptoms may be associated with other respiratory infections.[100] Currently, real time reverse transcriptase polymerase chain reaction (rRT-PCR) assay and chest imaging using CT scans are the primary diagnosing methods. Based on the common diagnostic criteria established by the China National Health Commission, laboratory molecular-based tests have become a standard tool for diagnosis of COVID-19 due to their accuracy in targeting and identifying particular pathogens.[101] This section highlights the common methods of COVID-19 detection including nucleic acid tests, chest imaging, and rapid kit test, including the advantages and drawbacks.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

Figure 2. Schematic of SARS-CoV-2 structure.

3.1. Nucleic Acid Diagnostic Tests

3.1.1. RT-PCR

PCR has become a standard diagnostic and research tool due to its capacity for providing quantitative genetic analysis of DNA and RNA.[102] Current diagnostic tests that have been the most frequently used for detecting COVID-19 are based on nucleic acid amplification methods, such as RT-PCR, real time (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP), with the former being considered the gold standard. In this assay, viral RNA extracted from patient samples (e.g., oro/nasopharyngeal swab, sputum, or bronchoalveolar lavage) is transcribed to complementary DNA (cDNA) and amplified by PCR (**Figure 3**A).[103] RT-PCR can be conducted as a one- or two-step assay to target the two main regions (ORF1b and N) of SARS-CoV-2. The major advantage to one-step reactions is the requirement for fewer manipulations, providing high-throughput analysis and a lower risk of cross-contamination.[104] The two-step assay is more sensitive and time-consuming, due to an extra open-tube step and pipetting manipulations, which can also result in greater variability and risk of contamination.[105]

RT-PCR assays use three different regions of SARS-CoV-2 genes, encoding the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N). The RT-PCR assays based on RdRp/Hel genes have high specificity as the PCR primers do not amplify other human coronaviruses (e.g., MERS and SARS).[106] Many RT-PCR assays have been approved by the Food and Drug Administration (FDA) with the most prominent being the Xpert Xpress SARS-CoV-2 test developed by Cepheid (USA) that detects SARS-CoV-2 virus in nasopharyngeal swab, nasal wash, or aspirate specimens in 45 min.[106,107] Vivalytic COVID-19 test is another RT-PCR assay developed by Bosch (Germany) and Randox Laboratories (United Kingdom) that enables detection in under 2.5 h and simultaneously detects SARS-CoV-2 with nine other respiratory viruses.[106] The recently introduced Abbott ID Now test provides results in 5 min, amplifying the RdRp gene. The test is designed for near-patient testing in any healthcare environment. Throat, nasal, nasopharyngeal, and oropharyngeal swabs can be used for sampling.[106]

Despite RT-PCR being the gold standard for COVID-19 diagnosis, there is a potential for false-negative results, and may be related to the viral load and the time of sampling. The RT-PCR results typically provide a positive result if specimen was collected 2–8 days postinfection.[108]

Although RT-PCR molecular tests have become standard tools for COVID-19 detection, there remain numerous challenges, including sample collection issues such as inappropriate or inadequate sample collection in terms of quality and volume, incorrect transportation and storage of samples (e.g., delay in transport or improper packaging and shipping methods), and presence of interfering substances (e.g., blood, nasal secretions, or mucus). Other challenges include the shortage of reagents and instrumentation, delays with the installation of instruments, and false-negative results ($\approx$30%).[109]

3.1.2. RT-LAMP

To increase testing rates, shorten turnaround times, and improve upon the limitations of RT-PCR, the one-step nucleic acid amplification method has been developed for diagnosing COVID-19 infections. LAMP is a single-tube and low-cost technique for the amplification of DNA following reverse transcription.[110] RT-LAMP has high specificity and sensitivity, operational simplicity, low cost, and results detectable by the naked eye in less than 1 h (Figure 3B).[110,111] RT-LAMP uses DNA polymerase and 4–6 primers including two inner primers (a forward and a reverse inner primer) and two outer primers, which chemically bind to six specific regions on the target genome, making this method highly specific with the higher number of primers.[112] Several RT-LAMP assays have been developed for COVID-19 detection. As an example, Lamb et al. recently developed a rapid screening RT-LAMP diagnostic test that could detect COVID-19 infections in less than 30 min.[110] They simulated patient samples by
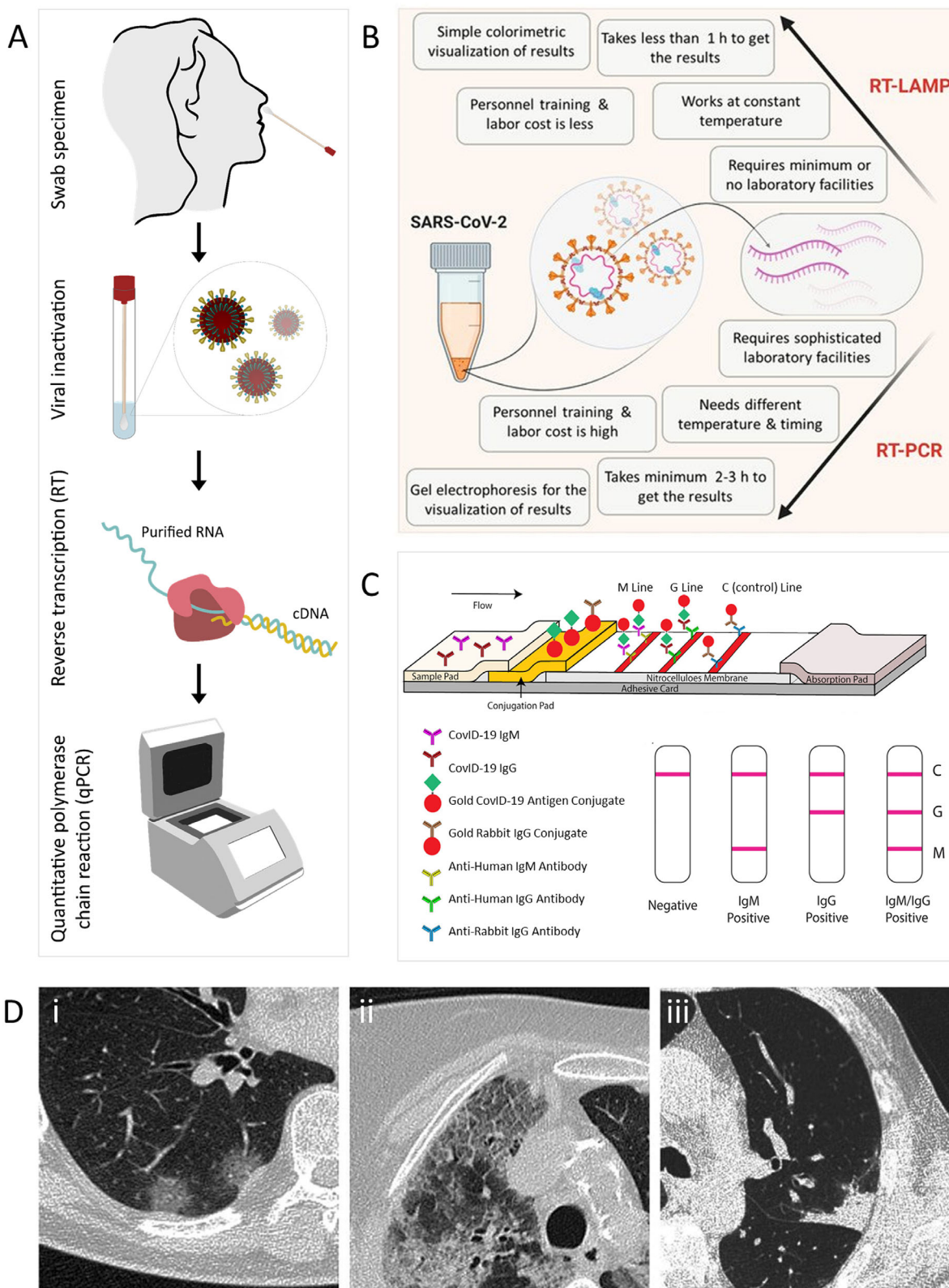
Figure 3. COVID-19 diagnostic tests. A) RT-PCR test procedure. B) Comparison and benefits of RT-LAMP and RT-PCR. Reproduced with permission.[160] Copyright 2020, MDPI C) Schematic illustration of rapid SARS-CoV-2 IgM-IgG combined antibody test. Adapted with permission.[161] Copyright 2020, John Wiley & Sons. D) Axial chest CT images of COVID-19 pneumonia showing i) GGO, ii) crazy-paving pattern, and iii) consolidation. Adapted with permission.[162] Copyright 2020, Springer.

**ADVANCED
SCIENCE NEWS**
www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**
www.advtherap.com

spiking different type of samples including serum, urine, saliva, oropharyngeal swabs, and nasopharyngeal swabs with a portion of the COVID-19 nucleic sequence. This simple and fast assay is portable and could be administered for various types of biological samples without specialty training or equipment. WarmStart Colorimetric LAMP 2X Master Mix is another prominent RT-LAMP assay, which contains a visible pH indicator for the rapid and easy detection of LAMP and RT-LAMP reactions. Amplification is easily detectable with a simple pink-to-yellow color change.[113]

In addition to isothermal amplification, there are other nucleic acid tests for the detection of COVID-19 infection. For example, SHERLOCK is a robust test that can detect COVID-19 using Cas13a ribonuclease for RNA sensing.[113] This technique showed almost single-copy sensitivity with a shorter turnaround time than RT-PCR and can be considered as a promising diagnostic option for the emerging pathogen.

3.2. Chest CT

Clinical diagnosis using CT imaging has played a vital role in the early detection and management of COVID-19, particularly in light of diagnostic test kit shortages and presumptive false-negative RT-PCR tests.[114] A chest CT scan involves taking measurements of X-ray attenuation through a cross-sectional plane of the thorax from different rotational angles. This data is then used to construct a digital cross-sectional image of the chest showing the different lobes of the lungs, and is particularly good for detailing soft tissues.[115] Multiple research groups have found that COVID-19 pneumonia manifests with visible abnormalities in chest CT images in both symptomatic and asymptomatic patients (Figure 3D).[116] This can be helpful in the early screening of suspected cases and for evaluating the severity of a case. The findings on chest CT scans in early-stage disease (day 0 to day 4 following the onset of symptoms) are prominently multiple patchy ground glass opacities (GGOs) with or without consolidation involving multiple lobes with peripheral distribution.[21,22,114] These initial GGO abnormalities can be accompanied by a halo sign, vascular enlargement in the lesion, crazy paving pattern, and/or an air bronchogram sign.[13,117] Zhao et al. determined that GGO lesions more commonly have bilateral involvement, are predominant in the lower lung, and are multifocal.[117] As the infection progresses past day 4, dense consolidation may become increasingly prevalent.[114]

The diagnostic value chest CT has been compared to RT-PCR assay by researchers Ai et al., who also investigated the consistency of the diagnostic CT findings within a sample group of 1014 patients.[24] The sensitivity of chest CT scans for diagnosing COVID-19 was found to be higher than RT-PCR. Additionally, 42% of cases showed improvements in follow-up chest CT scans, before the RT-PCR test results turned negative.[24] Similar findings by Fang et al. show a sensitivity of 98% for CT imaging, compared to a 71% sensitivity of RT-PCR.[26] Furthermore, Xie and co-workers report that 3% of 167 patients had a negative RT-PCR result for COVID-19 upon initial presentation, despite chest CT scan showing signs of viral pneumonia.[117] However, chest CT scan does not distinguish between different pneumonia viral infections as the imaging features of COVID-19 can overlap. The specificity of chest CT for diagnosis of COVID-19 is reported as

low as 25% by Ai et al.,[24] therefore, RT-PCR remains the gold standard for diagnosis of COVID-19.

The COVID-19 infection confirmed with RT-PCR may present with normal chest CT scan findings upon admission, however, the percentage of these patients varies clinically. When imaged up to 2 days following the onset of symptoms, 56% (20 of 26 patients) were found to have normal chest CT images,[85] while other research groups observed 2% (1 of 51 patients)[26] after symptom onset, and 3% (21 of 601 patients) tested positive with RT-PCR,[24] had initially normal CT scans. Pan et al. reported the 19% (4 of 21 patients) with an initially normal chest CT had visible lung abnormalities in repeated pulmonary CT scans, around 4 days after initial imaging.[114] This finding was limited to patients without severe respiratory disease or requiring oxygen treatment.

Findings by Yang and Yan showed that 11.4% (17 of 149 symptomatic patients) with normal chest CT at admission became COVID-19 positive after 7 days.[118] Thus, chest CT scans cannot be used to exclude a positive diagnosis of COVID-19, particularly in patients with early symptom onset. Medical and public health bodies in the United States and China have not adopted chest CT as a diagnosis method. Furthermore, the cost efficacy and radiation exposure of chest CT scans as a COVID-19 diagnostic tool must be examined. CT machines are expensive to run and maintain, may not be available in developing countries, and require specific technical expertise. However, it is important to note that the high virulence of COVID-19 makes identifying suspicious CT cases a priority to properly isolate potentially infected patients and deliver the appropriate treatment.

3.3. Rapid and Point-of-Care (POC) Diagnostic Methods

RT-PCR is established as the standard technique for molecular-based in vitro diagnostic (IVD) tests, but suffers from drawbacks including requirements for sophisticated laboratory, expensive equipment, and expert technicians for operation.[106,119,120] These conditions give the molecular-based analysis method a long turnaround time. Additionally, using conventional RT-PCR methods, early stage diagnosis of COVID-19 (up to 2 weeks) can cause false-negative results as insufficient viral RNA concentration can be found in the clinical samples during the early stages of infection.[108,106] The limitations of such molecular analysis methods restricts their application in pandemic conditions, which require rapid and in-field detection of infected individual to decrease disease propagation. Apart from the emerging advances in molecular-based assays for the detection of virus genomes in different clinical specimens, there are other potential diagnostic tests through which serological levels of antibodies or viral antigens are detected.[14,121,122] The COVID-19 outbreak highlights the importance of low-cost rapid and POC diagnostic tools that are accurate and sensitive for identification of infected cases. Such tests are required for better understanding the time course and transmission period of the disease and directly guiding efforts on virus propagation management.

Rapid and POC viral diagnostic kits are considered an analytical biosensor device through which the viral target (including proteins, antigens, RNA, or DNA) is detected in a fast, accurate, and sensitive response.[123–126] Given the advancements

**ADVANCED
SCIENCE NEWS**
www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**
www.advtherap.com

in nanotechnology, recently developed rapid detection kits enjoy benefits over conventional tests, including a low limit of detection (LOD), real-time analysis, and label-free detection.[127–129] Such advances result from new nanosystems that facilitate various receptor–ligand binding reactions and subsequently reduce the detection time. Rapid and POC diagnostic kits for COVID-19 are divided into two distinct groups; genomic diagnostic tests and immunodiagnostic tests.

3.3.1. Immunoassay-Based Rapid Tests

Immunoassay tests for COVID-19 diagnosis can detect virus antigen or SARS-CoV-2 specific host antibodies (immunoglobulins M and G (IgM and IgG) (Figure 3C). Serological methods like ELISA and lateral flow immunoassay (LFIA) are robust tests that are capable of detecting viral infections with short turnaround times.[107,130,131] LFIA is a powerful pathogen detection platform through which both viral biomarkers (virus specific antigens and associated antibodies) are detectable. With sufficient levels of the biomarker in a sample, a visible color change in the test and control zone indicates the positive results of the experiment. However, by using different nanoparticles (e.g., gold nanoparticles, nanoclusters, and polymers dots) for labeling chemistry, the interaction of the detection antibody on the strip and viral biomarker results in a specific signal that varies from optical to fluorescent signals with different sensitivity.[132,133] All LFIA-based tests detect either anti-SARS-CoV-2 IgG and IgM antibodies separately or the whole antibody (mainly IgM and IgG) within samples. IgM/IgG detection LFIA and ELISA kits for diagnosing COVID-19 have been produced by several companies and have shown higher throughput rates than nucleic acid assays (**Table 2**).

Xiao et al. have developed an ELISA test to detect the presence of SARS-CoV-2 antibodies by capturing IgM and IgG.[134] One of the other predominant and rapid POC lateral flow immunoassays is the BioMedomics (USA) COVID-19 IgM/IgG test, which can detect both early marker and late marker IgM/IgG antibodies in human finger-prick or venous blood samples. Another prospective POC serology-based test has been recently developed by Pharmacyt AG company (Germany). According to a study reported by Woo et al., the type of viral target for immunoassay detection affects the accuracy and sensitivity of the test; the sensitivity of SARS-CoV N-based IgG ELISA (94.7%) is significantly higher than that of SARS-CoV S-based IgG ELISA (58.9%).[135] Immune-associated antibodies (IgG and IgM) are typically the host immune cell's first response for fighting the virus, so that IgM appears within the first 5–7 days of the infection but fades toward the end. Following this step, IgG antibodies, hallmarks of humoral immune system maturation and long-term protection indicators, are produced in the serum and typically recruit other immune cells (e.g., macrophages) for clearing viral pathogens.[136] In this regard, most of the serological tests that only measure the level of IgM or IgG are unable to differentiate between a patient with an acute infection and a recovered patient. Herein, developing a quantitative LIFA assay with the capacity for IgM to IgG ratio measurement is a good approach for initially assessing a patient's immune status. Given that 20–80% of COVID-19 cases are estimated to be asymptomatic,[84] current antibody immunoassay tests are a suitable solution for monitoring and surveillance of the population in such a pandemic.

Direct antigen detection is an alternative method in which the presence of viral proteins expressed by the virus are detected in a collected sample. Unlike the previous method, where samples are restricted to the blood or serum of patients, various origins of the antigen are able to be used. Viral antigens can be directly detected in either finger-prick samples or saliva. In this regard, Sona Nanotech Inc. (Canada) has recently developed a rapid LIFA kit that actively produces a signal when exposed to COVID-19 viral antigens. However, obstacles such as low viral concentrations in the collected specimens or a lack of high-quality specimen collection may impact the sensitivity of the experiment, varying between 34% and 80%.[137] In this regard, LEADGENE Co. (South Korea) has developed a modified rapid antigen kit with a turnaround time of 10 min and higher sensitivity without cross-reactivity to MERS and general coronaviruses. According to the WHO, the majority of the developed antigen/antibody assay kits could potentially be used as triage tests to rapidly screen likely COVID-19 positive patients, so there is an urgent need to develop multiplex testing methods that can detect several biomarkers in a single test. These innovations would enable health providers to not only detect the acute infected cases at early stages, but also detect the severity level of the disease and period of infection, which can have a positive impact on the further spread of infection. Moreover, further integration of nanochemistry and disposable microdevices can contribute to biosensor platforms with sensitive and accurate quantitative results for analyzing the viral load in infected patients.

3.3.2. Genomic Assay-Based Rapid Tests

A promising method that enables the rapid detection of SARS-Cov-2 targets multiple regions of the viral genome through a multiple gene assay. This method has been adopted by Chu et al.; a single step RT-PCR assay detects ORF1b and N regions of SARS-CoV-2 in 1 h and 15 min, respectively.[101] Accula SARS-CoV-2 test is another molecular rapid test that uses throat and nasal swab samples in an automated RT-PCR handheld cartridge, with results given after 30 min.[148] ePlex SARS-CoV-2 has also developed a rapid molecular test with a qualitative nucleic acid multiplex assay, conducted on a single use cartridge, where results are reported in 2 min.[149] As described above, LAMP is a powerful method that facilitates platforms for rapid molecular diagnosis of SARS-CoV-2. Abbott ID-now technology is the most recent FDA emergency-approved rapid molecular POC test that can deliver positive results in as few as 5 min and negative results in 13 min. This test utilizes the LAMP technology method to target the RdRp gene in the genome profile of SARS-CoV-2[150] Another effort in this field was made by Milenia Biotec (Germany) with the development of the HybriDetect method, where different molecules, including gene amplification products, proteins, and antibodies, are rapidly detected on a lateral flow dipstick (LFD). Using this method, the sample-to-answer process takes ≈30 min. To prove the HybriDetect method for rapid detection of SARS-CoV-2, Broughton et al. developed the SARS-CoV-2 DNA endonuclease-targeted CRISPR trans reporter (DETECTR) assay.[151] This assay performs simultaneous RT-LAMP for RNA extraction from

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

Table 2. Immunoassay diagnostic tests for COVID-19.

Company	Product name	Sample type	Detectable factor	Detection method	Phase of development	Advantages	Disadvantages	Refs.
RayBiotech (USA)	Coronavirus (COVID-19) IgM/IgG Rapid Test Kit	• Human serum • Plasma • Whole blood • Finger prick	IgG antibodies	Lateral flow assay and ELISA	Approved for research use under FDA EUA in US	• Results ready in ≤20 min • High sensitivity • S and N protein receptor binding of IgG antibody (in ELISA)	• Testing limited to healthcare and pharmaceutical professionals • Requires special training • Not IgM antibody detection	[138]
Cellex Inc (USA)	Cellex qSARS-CoV-2 IgG/IgM Rapid Test	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	FDA and EUA for diagnostics	• Easy to use • Results ready in 15–20 min	• Testing limited to healthcare and pharmaceutical professionals • Unknown test sensitivity early after infection • Test results must read between 15–20 min after a specimen is applied to the sample well	[139]
Aytu BioScience (USA/China)	COVID-19 Rapid Test	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	CE approved, awaiting FDA approval	• Results ready in 2–10 min at the POC	• ≈91.9% sensitivity • Follow-up testing with a molecular diagnostic should be considered • Fresh samples only	[140]
Wondfo Biotech Co., Ltd. (China)	Finecare SARS-CoV-2 Antibody Test	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	CE/IVD in China	• Small specimens (5 μL of serum/plasma or 10 μL of whole blood) • Results ready in 10 min • High sensitivity and specificity	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[141]
Dynamiker (China)	2019 nCOV Rapid Test	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	Not FDA approved	• Ease of use • Results ready in 10 min	Testing limited to healthcare and pharmaceutical professionals Requires special training	[142]
Boditech (Korea)	ichroma COVID-19 Ab	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Fluorescent lateral flow assay	Not FDA approved	• Results ready in 10 min • Results are semiquantitative as positive, intermediate, or negative	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[143]
Advaite (USA)	RapCov	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	Emergency FDA request pending	• Ease of use • Results ready in ≤15 min	• 88% sensitivity • Testing limited to healthcare and pharmaceutical professionals	[144]
Sona Nanotech Inc. (USA)	Rapid COVID-19 Test	• Human serum • Plasma	Virus antigen	Lateral flow assay	Expected regulatory relief by FDA	• Results ready in 5–15 min • Costs less than $50 • No specialized laboratory equipment or technicians required	N/A	[145]

(Continued)

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

Table 2. Continued.

Company	Product name	Sample type	Detectable factor	Detection method	Phase of development	Advantages	Disadvantages	Refs.
LEADGENE (Taiwan)	SARS/SARS-CoV-2 Antigen Rapid Test	• Nasopharyngeal swab specimens • Nasopharyngeal wash or aspirate	Virus antigen	Lateral flow assay	Not FDA approved	• Viral antigen detection • Results ready in 10–15 min • No cross-reactivity	Research use only	[139]
Epitope Diagnostics Ltd. (USA)	KT-1032 KT-1033 KT-1034	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	ELISA	Not FDA approved	• High accuracy and sensitivity	• Testing limited to healthcare and pharmaceutical professionals • Requires special training • Two separate kits for IgG and IgM detection	[140]
Creative Diagnostics (USA)	SARS-CoV-2 IgG/IgM ELISA Kit SARS-CoV-2 antigen ELISA Kit	• Human serum • Plasma	Nucleoprotein/ NP protein or Patient IgG that reacts to N protein	ELISA	Not FDA approved	Capability of direct virus antigen testing Quantitative results in antigen testing	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[141]
BTNX (Canada)	COV-13C25	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	Not FDA approved	High accuracy	• Testing limited to healthcare and pharmaceutical professionals • Not for the screening of donated blood	[146]
Sugentech (South Korea)	COVID-19 IgM/IgG kit	• Human serum • Plasma • Whole blood	IgG/IgM antibodies	Lateral flow assay	CE Mark, FDA approved	• Results visually observable within 10 min	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[147]
MyBioSource (USA)	Human COVID-19 IgG/IgM Antibody ELISA Kit	Human serum	IgG/IgM antibodies	ELISA	FDA approved	• High accuracy and sensitivity	• Testing limited to healthcare/pharmaceutical professionals • Time consuming sample preparation • Sample type limited to serum, which must be collected with no bacteria	[144]

respiratory swab samples in universal transport medium (UTM), followed by the detection of Cas12, a predefined coronavirus sequence. This CRISPR-based DETECTR method provides a visual and faster alternative to the RT-PCR assay with 95% positive and 100% negative predictive agreement for COVID-19 detection. **Table 3** summarizes the genomic assay-based tests for COVID-19 detection.

4. Treatment Strategies

4.1. Current Therapies

According to the WHO documentation for clinical management of severe acute respiratory infection[140] and the Chinese National Health Commission documentation for diagnosis and treatment of pneumonia caused by COVID-19 v7.0,[141] when COVID-19 disease is suspected, symptomatic and respiratory

support must be the main focal points for COVID-19 treatments. WHO guidelines recommend the following for the management of COVID-19 and the associated clinical symptoms: adults and children with severe pneumonia and severe acute respiratory infection (SARI), acute respiratory distress syndrome (ARDS), hypoxaemia, or shock should be given supplemental oxygen therapy. Co-infections causing SARI and sepsis should have treated with empiric antimicrobials. Extracorporeal membrane oxygenation (ECMO) is also recommended for patients with refractory hypoxemia.[140] As health organizations do not currently recognize any specific anti-COVID-19 treatments for patients with confirmed cases of COVID-19,[140] the few published clinical trials, descriptive reports, and clinical treatment experiences must be carefully evaluated as clinical outcomes and mortalities will differ widely with shifting demographics. **Table 4** highlights potential therapeutics for the treatment of COVID-19. The cut-off date for the following reported data is July 2020. Future randomized

Table 3. Genomic assay-based tests for COVID-19.

Company	Product name	Sample type	Detectable biomarker	Detection method	Phase of development	Advantages	Disadvantages	Refs.
Bosch (DE)	Vivalytic-rapid-test-for-COVID-19	• Nose/throat swab	Viral DNA	Multiplex PCR and μ-array	EU (CE Mark)	• Patient sample can be tested for nine other respiratory viruses (not including SARS-CoV-2) • Fully automated sample processing	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[152]
Partnership: Cepheid (USA), Sherlock Biosciences (USA)	GeneXpert + SHERLOCK	N/A	Viral DNA/RNA	CRISPR-Cas12/Cas13-based test	Proof-of-concept for broad product development	• Sample cartridge ease-of-use	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[153]
CASPR Biotech (USA)	N/A	N/A	Synthetic SARS-CoV-2 RNA sequences	CRISPR-Cas12-based test	Proof of principle evaluation	• High sensitivity • Rapid detection (<1 h) • Paper-based testing strips are portable and administrable in public	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[154]
Cepheid (USA)	Xpert Xpress SARS-CoV-2	• Nasal swab	Viral RNA	Nucleic acid technology (real-time qPCR)	FDA emergency use authorization	• Results returned in ≈45 min • Uses disposable cartridges prefilled with the required chemicals, which are channeled around test chambers using microfluidics • Does not require a lab facility or special training to operate	• Testing limited to healthcare and pharmaceutical professionals	[155]
Abbott (USA)	ID NOW COVID-19	• Nasal swab	Viral RNA	Isothermal nucleic acid amplification (LAMP)	FDA emergency use authorization	• High sensitivity • Results returned in <5 min	• Testing limited to healthcare and pharmaceutical professionals	[156]
1drop Inc. (KR) & Luminarie Canada Inc.	1copy COVID-19 qPCR Multi Kit	• Nasopharyngeal swab/oropharyngeal swab	Viral RNA	Nucleic acid technology	FDA approved and commercialized	• High sensitivity (limit of detection of 200 genome copies mL^{-1}, equivalent to 4 genome copies per PCR reaction) • Short measurement time (<2 h)	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[157]
Thermo Fisher (USA)	TaqPath COVID-19 Combo Kit	• Nasopharyngeal swab • Nasopharyngeal aspirate • Bronchoalveolar lavage (BAL) specimens	Viral RNA	Nucleic acid technology (real-time PCR)	FDA approved and commercialized	• Targeted specificity to 100% of currently available complete genomes for SARS-CoV-2	• Testing limited to healthcare and pharmaceutical professionals • Improper collection, transport, or specimen storage may reduce accuracy • Nonspecific to SARS-CoV-2 diagnostic report generation in <4 h	[158]
InBios (USA)	Smart Detect SARS-CoV-2 rRT-PCR Kit	• Nasopharyngeal swab • Anterior nasal swab • Mid-turbinate nasal swab	Viral RNA	Nucleic acid technology (real-time PCR)	FDA emergency use authorization	• High accuracy • High sensitivity	• Testing limited to healthcare and pharmaceutical professionals • Requires special training • Results take around 4 h	[159]

(Continued)

Table 3. Continued.

Company	Product name	Sample type	Detectable biomarker	Detection method	Phase of development	Advantages	Disadvantages	Refs.
Anatolia Geneworks (TU)	Bosphore Novel Coronavirus (2019-nCoV) Detection Kit	• Human respiratory samples	Viral RNA	Nucleic acid technology (real-time PCR)	EU (CE Mark)	• High specificity • No cross-reactivity to other viruses	• Testing limited to healthcare and pharmaceutical professionals • Requires special training	[158]

Table 4. Potential therapeutics for the treatment of COVID-19.

Treatment category	Drug(s)	Description of treatment	Stage of development for COVID-19	Refs.
Respiratory support	–	Supplemental oxygen therapy	Approved	[140]
Oxygenation support	–	ECMO	Approved	[140]
Corticosteroid	Budesonide–formoterol	200/6 μg inhaled BID for 30 days	Investigational, Phase 3	NCT04331054
Antiviral	Remdesivir	Intravenous infusion of 200 mg, followed by 100 mg for 10 days	Authorized for emergency use	NCT04280705, NCT04292730, NCT04292899
Antiviral	Lopinavir–ritonavir	400 mg lopinavir + 100 mg ritonavir orally BID for 14 days	Investigational, Phase 3	NCT04321174[172]
Antiviral	Chloroquine–hydroxychloroquine	10 mg base kg^{-1} loading dose, 155 mg QD for 3 months	Investigational	NCT04303507
Antiviral	Arbidol	2 tablets/time, 3× per day for 14–20 days	Investigational, Phase 4	NCT04260594
Antiviral	Nafamostat	–	Preclinical testing	[21]
Antiviral	Nitazoxanide–hydroxychloroquine	500 mg BID + 200 mg HCQ BID for 10 days	Investigational, Phase 4	NCT04341493
Antiviral	Favipiravir	1800 mg 2× day 1, followed by 800 mg BID days 2–14	Authorized for emergency use	NCT04434248
Antiviral	Baricitinib	4 mg QD orally + 300 mg BID ritonavir for 2 weeks	Investigational, Phase 3	NCT04320277
Convalescent plasma	COVID-19 CP	Single dose 300 mL CP infusion	Investigational, Phases 2,3	NCT04342182
Vaccine	mRNA-1273	Encodes for full-length, perfusion stabilized spike protein of SARS-CoV-2	Investigational, Phase 2	[32,180]
Vaccine	COVID-19 S-Trimer	Targets native trimeric viral spike protein on the viral envelope of SARS-CoV-2	Investigational	[31]
Vaccine	MVA-VLP	Multiprotein structure mimics the organization and conformation of SARS-CoV-2	Investigational	[80]
Vaccine	Measles	Cross-reactivity with SARS-CoV-2	Approved	[197]

control trials are required to support the efficacy and safety of alternative COVID-19 therapies.

4.2. Corticosteroids

Several conflicting reports have stated that COVID-19 symptoms can be exacerbated with or without the use of corticosteroids.[163] Corticosteroids are involved in key physiological processes such as the immune and inflammatory responses and are commonly prescribed at low dosages to patients with suppressed immune systems. In the recently published clinical management report,

WHO does not currently support the use of corticosteroids as a COVID-19 treatment option.[147] However, corticosteroids were widely used during SARS-CoV[164] and MERS-CoV[165] outbreaks to modulate the inflammatory responses of the lungs and immunopathological damage. A systematic review of community-acquired pneumonia (CAP) suggests that corticosteroid use could reduce mortality rates and the need for mechanical ventilation for patients with community-acquired pneumonia.[166]

A retrospective cohort study by Zhou et al. looked at 813 adult patients with varying levels of systematic corticosteroid treatments given 10–16 days after COVID-19 symptom onset. Researchers hypothesized that high-dose corticosteroid may have

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

contributed to poor clinical outcomes.[167] Alternatively, the low-dosage use of methylprednisolone for severe COVID-19 pneumonia was associated with faster clinical improvements.[168] The ongoing randomized clinical trial (NCT04331054) will focus on the use of an inhaled steroid therapy and β_2 adrenergic agonist, commonly prescribed to asthmatic individuals, for a local protective effect against SARS-CoV-2 infection in terms of time to clinical improvement. Concerns regarding the use of corticosteroids as therapeutics include secondary infections, long-term complications, and prolonged virus shedding.[163] As existing evidence remains inconclusive, future randomized controlled trials are needed to determine the safety and efficacy of corticosteroid treatment recommendations.

4.3. Antiviral Drugs

4.3.1. Pre-Existing Antiviral Drugs

The administration of antiviral drugs immediately after the onset of COVID-19 symptoms can stem contagiousness by reducing viral shedding in respiratory secretions, given that the viral load in sputum can last up to 2 weeks.[169] Typical antiviral drugs include neuraminidase, ganciclovir, acyclovir, ribavirin, and methylprednisolone, none of which is yet recommended for the treatment of COVID-19.[170]

Preliminary trials have begun on coformulations of protease inhibitors lopinavir–ritonavir, drugs currently used in controlling infections caused by the human immunodeficiency virus (HIV-1).[171] Lim et al. suggest that lopinavir–ritonavir could decrease the shedding of SARS-CoV-2 virus; however, larger studies have failed to confirm these observations.[171,172] A Phase 3 randomized clinical trial (NCT04321174) on the effectiveness of lopinavir–ritonavir dosage is ongoing and due for completion in 2022.

CQ and hydroxychloroquine (HCQ) have been extensively used for the treatment of malaria and chronic inflammatory diseases. While both have shown antiviral activity against SARS-CoV-2 in vitro,[173] multiple recent randomized control trials have failed to confirm the effectiveness of these drugs in treating patients hospitalized for COVID-19.[174–176] An uncontrolled study with a smaller sample size of 26 patients showed that HCQ treatment was associated with significant viral load reduction, in addition to a synergistic effect when combined with azithromycin,[177] while a second uncontrolled trial demonstrated no such viral clearance in severe COVID-19 patients with combination drugs therapy.[178] Of note, a double-blind, randomized, placebo-controlled trial of CQ against HCQ for the prevention of severe COVID-19 symptoms (NCT04303507) is currently being planned, with the involvement of 40 000 participants.

Remdesivir demonstrates broad-spectrum antiviral activity against some RNA viruses.[179] In an in vitro study, Wang et al. showed that remdesivir efficiently inhibited virus infection in human liver cancer cell line Huh-7, which is sensitive to SARS-CoV-2.[34] Researchers Grein et al. prescribed intravenous remdesivir (GS-5734) on a compassionate-use basis to patients hospitalized with severe COVID-19 days (i.e., low oxygen saturation and/or required mechanical ventilation) for a total of 10 days.[179] Clinical improvement was observed in 68% of patients and the mortality rate in the cohort was lower than those reported in other countries, however, outcomes for 50% of the patients were yet to be determined at date of publication. Three existing Phase 3 clinical trials are ongoing for the evaluation of remdesivir in patients with mild to severe COVID-19, including NCT04280705, NCT04292730, and NCT04292899. The adaptive, randomized, double-bind, placebo-controlled adaptive COVID-19 treatment trial (NCT04280705), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), will evaluate the clinical severity, hospitalization, and mortality of patients, compared to a control. Based on a topline data review of this trial, the unapproved product remdesivir has been authorized for emergency use by the FDA for the treatment of patients hospitalized with severe COVID-19, as of May 2020.

Other antiviral drugs being evaluated for off-label use for SARS-CoV-2 infection are nafamostat, nitazoxanide, favipiravir, baricitinib (NCT04320277), and arbidol (NCT04260594). In vitro studies showed that both nafamostat and nitazoxanide blocked SARS-CoV-2 replication and infection.[21] Nitazoxanide will be tested in combination with HCQ in a Phase 4 clinical trial (NCT04341493), to contrast the beneficial effect of nitazoxanide when combined with other drugs. A limited nonrandomized study where patients were treated for 9 days with arbidol showed lower mortality rates and shorter hospital discharge rates.[66] Favipiravir was compared with arbidol in a randomized multi-center study. Differences in clinical recovery were observed with moderate infections, with favipiravir contributing to significant relief from pyrexia and cough.[180] Initially marketed as an anti-influenza agent with inhibition of 53 strains of influenza, favipiravir has received approval for emergency use in more than 10 countries. The optimal clinical dosage of favipiravir has been difficult to establish from the limited preclinical and in vitro data of SARS-CoV-2, however higher dosages have been required to inhibit infection in epithelial Vero cells.[34] An ongoing Phase 3 trial has shown that, after 3 days of high-dose favipiravir treatment, fever returned to baseline normal in 70% of recruited patients when compared to the standard of care group (NCT04434248). During the pivotal phase of this trial, a favipiravir dosage will be selected based on observations of viral elimination by day 10, time to viral elimination within 1 month, and time to clinical improvement.

4.3.2. Novel Antiviral Candidates

The current ongoing efforts in the development of new antiviral drugs has been driven by the global need for effective therapeutic options. Researchers at the Emory Institute for Drug Development (EIDD) have recently discovered the prophylactic EIDD-2801, which was tested in vitro on human lung cells infected with SARS-CoV-2 and in vivo in mice infected with the related SARS-CoV and MERS-CoV coronaviruses.[181] EIDD-2801 can reduce the degree of lung damage and weight loss in mice when given as a treatment 12–24 h after infection onset. This window of opportunity is expected to extend with humans, as the period between coronavirus disease onset and death is generally longer in humans, comparatively. Additionally, Pfizer (USA) has begun Phase 1 clinical trials on small molecule antiviral PF-07304814, which targets the 3CL protease

of coronaviruses.[182] PF-07304814 must be given intravenously at high dosages (500 mg per day), which may limit its use in hospital settings. However, researchers also tested the antiviral in conjunction with remdesivir as a combination antiviral therapy for increased efficacy and reduced resistance. In vitro data suggested that lower concentrations of each compound allowed for a similar level of control over coronaviruses in cells. Further, Selva Therapeutics (USA) has developed a novel small molecule antiviral therapy SLV213 (administered orally or intravenously) with activity against a broad range of viruses by inhibiting host cell cysteine proteases (cathepsin L) and preventing entry and reproduction of the virus.[183] Additional data has shown that SLV213 is highly potent against SARS-CoV-2, while preclinical investigational new drug (IND)-enabling safety studies have been completed. Phase 1 clinical testing of SLV213 for SARS-CoV-2 has been scheduled for the third quarter of 2020.

4.4. Immunoglobulin Therapy

In March 2020, the FDA issued recommendations to initiate studies on the administration of investigational convalescent plasma (CP) collected from patients who had recovered and were symptom-free from COVID-19 for 28 days.[82] The use of CP or hyperimmune immunoglobulins as a viral treatment has been studied in outbreaks of multiple respiratory infections including SARS-CoV-1,[184] H1N1 influenza,[185] and MERS-CoV,[186] with improved patient outcomes due to the enhanced viral clearance mediated by neutralizing antibodies.

The first reported COVID-19 CP trial by Shen et al. featured an uncontrolled case series, resulting in improved clinical status following the administration of CP in five critically ill patients 10–22 days after admission.[187] Additionally, high dosage intravenous IVIg (blood product containing polyclonal immunoglobulin G) was given to 3 patients over 5 days, as a potent immune modulator.[163] All patients clinically improved after administration; body temperature normalized in 1–2 days and breathing difficulties alleviated in 3–5 days. However, this report was limited by the small number of patients and existing confounding factors. Recently, a study by Duan et al. showed that CP was well tolerated in 10 severe adult cases of COVID-19 and led to the disappearance of viremia within 7 days.[188] After 3 days of treatment, clinical symptoms and paraclinical criteria rapidly improved. Two clinical trials on the use of CP, NCT04342182 and NCT04333355, are currently in progress. Notably, the Phases 2–3 randomized comparative trial NCT04342182 will observe patients given 1 dose of 300 mL CP from COVID-19 recovered donors for 60 days or until discharge.

While COVID-19 CP is not yet FDA approved and is only an investigational product, these results illustrate the promising use of CP for treating severe COVID-19 infections. Further randomized trials are still warranted to determine the optimal dosage, time-point, and clinical benefits.

4.5. Vaccines

Vaccinations using antigens that are pathogen specific can prevent viral infection or reduce disease severity, thereby reducing viral transmission. While there is no current vaccine for COVID-19, strategies employed to develop the experimental SARS-CoV and MERS-CoV vaccines may prove beneficial for SARS-CoV-2 vaccine development. Inactive virus, live-attenuated virus, viral DNA vectors, subunit vaccines, recombinant proteins, and DNA-based vaccines were developed following the 2002–2004 outbreaks of SARS-CoV[189–192] and tested in various live animal models including mice and hamsters. Similar development approaches were taken for the development of experimental MERS-CoV vaccines.

SARS-CoV-2 vaccines currently being tested include an investigational lipid nanoparticle (LNP) encapsulated mRNA-1273 vaccine, which has completed Phase 1 trials in 45 adult participants.[32,175] Interim analysis shows the promise of mRNA-based vaccines, given their advantages of shorter development and production cycles and high potency.[193] Early results of the Moderna COVID-19 vaccine have shown positive results; all eight vaccinated participants developed neutralizing antibodies to the virus, exceeding the levels seen in patients who had recovered from the virus naturally.[180] Based on these results, the Moderna Phase 2 trial will be amended to two dose levels, with the aim of selecting a pivotal vaccine dosage. A recombinant protein-based vaccine that is based on the native trimeric spike protein on the SARS-CoV-2 envelope (COVID-19 S-Trimer) is under development.[31] Production of this vaccine is carried out in rapid mammalian cell-culture based expression system.[194] Further, GeoVax Labs, Inc. are developing a modified vaccinia Ankara-virus-like particles (MVA-VLPs) vaccine platform.[80] VLPs are multiprotein structures that mimic the organization and conformation of the native SARS-CoV-2 virus but lack the viral genome, making them potentially safer templates with favorable production costs.[195]

Vaccines typically activate specific immunological responses to specific targeted pathogens. Interestingly, the measles vaccine has proven to increase the immune system's ability to fight off other pathogens. The antigen-sharing similarities between SARS-CoV-2 and measles are hypothesized to cause cross-reactivity between the eventual two vaccinations.[196] This cross-reactivity was observed from the reduced vulnerability of young populations compared to elderly populations in COVID-19 epicenters China and Italy. Italy has a significantly lower measles vaccine coverage than China (84.5% population coverage).[197] Comparatively, observations have been made that China (99% coverage),[198] has significantly lower COVID-19 cases and COVID-19 associated deaths with respect to population levels.[147]

The most adequate strategy for the long-term prevention of COVID-19 outbreaks is the development of a vaccine with widespread protective immunity. However, the development and testing of a vaccination requires ≈12–18 months before becoming available to the public. It is therefore necessary for research groups to continue investigations into alternative therapeutic options and the cross-resistant features of pre-existing vaccines.

5. Conclusion and Perspective

COVID-19 disease, a severe acute respiratory illness, has emerged as a serious global public health concern. Coronaviruses

are a family of viruses that are zoonotic, meaning they are transmitted between animals and people, and can result in various diseases ranging from the common flu to more severe acute respiratory illnesses such as MERS and SARS. It is likely that the main route of COVID-19 transmission (human-to-human) will continue to occur. Rapid and accurate detection of the causative viral pathogens of respiratory tract infections is important for the management of this novel pandemic, in addition to the study of appropriate treatment methods, clinical and governmental actions to reduce the spread, and management of the negative economic impacts of COVID-19, globally.

Based on the latest guidelines issued by the WHO, laboratory molecular PCR based tests such as RT-PCR have become a standard tool for confirmation of COVID-19. These technologies are first line weapons in the fight against an outbreak. The next research step has been the development of serological tests for their ease-of-operation, efficiency, and use as supporting diagnostic methods for nucleic acid tests for viral diagnosis. Such technologies are now playing an important role in identifying and managing the spread of COVID-19. However, it should be noted that these methods have showed misclassification errors and false negative results, errors that may be due to factors such as the quality and quantity of the collected samples, incorrect transportation and storage condition of samples, presence of interfering substances, and the time point during infection when the sample is collected. Chest CT scans are a common imaging tool with higher sensitivity for COVID-19 infection when compared to RT-PCR but have diagnostic overlap with other viral pneumonia. Chest CT can be used in combination with RT-PCR assays for individuals with high clinical suspicion of infection but negative RT-PCR results.

The novel coronavirus COVID-19 causes serious respiratory illness and has proved fatal in severe cases. While many COVID-19 therapeutic clinical trials are active and ongoing, considerable research efforts have been launched to investigate potential treatments including novel and pre-existing antiviral drugs, corticosteroids, convalescent plasma, and different vaccination strategies. However, no anti-COVID-19 treatments are currently recognized by the WHO, and the clinical outcomes of specific therapies for the treatment of this novel virus will not be available for some time. Therefore, current clinical treatments are focused on supporting respiration and alleviating symptoms. In addition, vigorous awareness, societal precautions, and surveillance are highly recommended for managing this life threatening virus.

Conflict of Interest

The authors declare no conflict of interest.

[1] WHO, Coronavirus Disease 2019 (COVID-19): Situation Report, 104, World Health Organization, Geneva **2020**.

[2] F. Wu, S. Zhao, B. Yu, Y. M. Chen, W. Wang, Z. G. Song, Y. Hu, Z. W. Tao, J. H. Tian, Y. Y. Pei, M. L. Yuan, Y. L. Zhang, F. H. Dai, Y. Liu, Q. M. Wang, J. J. Zheng, L. Xu, E. C. Holmes, Y. Z. Zhang, *Nature* **2020**, *579*, 265.

[3] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, *Nature* **2020**, *579*, 270.

[4] Y. M. Arabi, S. Murthy, S. Webb, *Intensive Care Med.* **2020**, *46*, 833.

[5] E. J. Emanuel, G. Persad, R. Upshur, B. Thome, M. Parker, A. Glickman, C. Zhang, C. Boyle, M. Smith, J. P. Phillips, *N. Engl. J. Med.* **2020**, *382*, 2049.

[6] G. Grasselli, A. Pesenti, M. Cecconi, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 1545.

[7] N. Fernandes, Economic effects of coronavirus outbreak (COVID-19) on the world economy, https://ssrn.com/abstract=3557504 or https://doi.org/10.2139/ssrn.3557504 (accessed: March 2020).

[8] W. J. McKibbin, R. Fernando, The global macroeconomic impacts of COVID-19: Seven scenarios, https://ssrn.com/abstract=3547729 or https://doi.org/10.2139/ssrn.3547729 (accessed: March 2020).

[9] J. Qiu, B. Shen, M. Zhao, Z. Wang, B. Xie, Y. Xu, *Gen. Psychiatry* **2020**, *33*, e100213.

[10] K. G. Andersen, A. Rambaut, W. I. Lipkin, E. C. Holmes, R. F. Garry, *Nat. Med.* **2020**, *26*, 450.

[11] J. F. Chan, S. Yuan, K. H. Kok, K. K. To, H. Chu, J. Yang, F. Xing, J. Liu, C. C. Yip, R. W. Poon, H. W. Tsoi, S. K. Lo, K. H. Chan, V. K. Poon, W. M. Chan, J. D. Ip, J. P. Cai, V. C. Cheng, H. Chen, C. K. Hui, K. Y. Yuen, *Lancet* **2020**, *395*, 514.

[12] V. M. Corman, D. Muth, D. Niemeyer, C. Drosten, *Adv. Virus Res.* **2018**, *100*, 163.

[13] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, *Lancet* **2020**, *395*, 507.

[14] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, *Lancet* **2020**, *395*, 497.

[15] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 1061.

[16] Y.-Y. Zheng, Y.-T. Ma, J.-Y. Zhang, X. Xie, *Nat. Rev. Cardiol.* **2020**, *17*, 259.

[17] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, *N. Engl. J. Med.* **2020**, *382*, 727.

[18] S. Su, G. Wong, W. Shi, J. Liu, A. C. Lai, J. Zhou, W. Liu, Y. Bi, G. F. Gao, *Trends Microbiol.* **2016**, *24*, 490.

[19] A. Wu, Y. Peng, B. Huang, X. Ding, X. Wang, P. Niu, J. Meng, Z. Zhu, Z. Zhang, J. Wang, *Cell Host Microbe* **2020**, *27*, 325.

[20] T. T.-Y. Lam, M. H.-H. Shum, H.-C. Zhu, Y.-G. Tong, X.-B. Ni, Y.-S. Liao, W. Wei, W. Y.-M. Cheung, W.-J. Li, L.-F. Li, G. M. Leung, E. C. Holmes, Y.-L. Hu, Y. Guan, *Nature* **2020**, *583*, 282.

[21] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W. J. Liu, D. Wang, W. Xu, E. C. Holmes, G. F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, *Lancet* **2020**, *395*, 565.

[22] Y. Wang, H. Kang, X. Liu, Z. Tong, *J. Med. Virol.* **2020**, *92*, 538.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

[23] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, *J. Pharm. Anal.* **2020**, *10*, 102.

[24] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun, L. Xia, *Radiology* **2020**, *296*, 200642.

[25] Y. Li, L. Xia, *Am. J. Roentgenol.* **2020**, *214*, 1280.

[26] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang, W. Ji, *Radiology* **2020**, *296*, 200432.

[27] X. Cai, J. Chen, J. Hu, Q. Long, H. Deng, K. Fan, P. Liao, B. Liu, G. Wu, Y. Chen, Z. Li, K. Wang, X. Zhang, W. Tian, J. Xiang, H. Du, J. Wang, Y. Hu, N. Tang, Y. Lin, J. Ren, L. Huang, J. Wei, C. Gan, Y. Chen, Q. Gao, A. Chen, H. He, D. Wang, P. Hu, F. Zhou, A. Huang, P. Liu, D. Wang, *J. Infect. Dis.* **2020**, *222*, 189.

[28] J. Xiang, M. Yan, H. Li, T. Liu, C. Lin, S. Huang, C. Shen, medRxiv 2020.2002.2027.20028787 **2020**, https://doi.org/10.1101/2020.02.27.20028787.

[29] W. Zhang, R. H. Du, B. Li, X. S. Zheng, X. L. Yang, B. Hu, Y. Y. Wang, G. F. Xiao, B. Yan, Z. L. Shi, P. Zhou, *Emerging Microbes Infect.* **2020**, *9*, 386.

[30] C. Liu, Q. Zhou, Y. Li, L. V. Garner, S. P. Watkins, L. J. Carter, J. Smoot, A. C. Gregg, A. D. Daniels, S. Jervey, D. Albaiu, *ACS Cent. Sci.* **2020**, *6*, 315.

[31] L. Deng, C. Li, Q. Zeng, X. Liu, X. Li, H. Zhang, Z. Hong, J. Xia, *J. Infect.* **2020**, *81*, e1.

[32] A. Maxmen, *Nature* **2020**, *578*, 347.

[33] P. Richardson, I. Griffin, C. Tucker, D. Smith, O. Oechsle, A. Phelan, J. Stebbing, *Lancet* **2020**, *395*, e30.

[34] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, *Cell Res.* **2020**, *30*, 269.

[35] Y. Liu, A. A. Gayle, A. Wilder-Smith, J. Rocklöv, *J. Travel Med.* **2020**, *27*, taaa021.

[36] S. Perlman, J. Netland, *Nat. Rev. Microbiol.* **2009**, *7*, 439.

[37] B. T. Bradley, A. Bryan, *Semin. Diagn. Pathol.* **2019**, *36*, 152.

[38] C. S. Goldsmith, K. M. Tatti, T. G. Ksiazek, P. E. Rollin, J. A. Comer, W. W. Lee, P. A. Rota, B. Bankamp, W. J. Bellini, S. R. Zaki, *Emerging Infect. Dis.* **2004**, *10*, 320.

[39] World Health Organization, Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003, http://www.who.int/csr/sars/country/table2004_04_21/en/index.html (accessed: **2003**).

[40] V. C. Cheng, S. K. Lau, P. C. Woo, K. Y. Yuen, *Clin. Microbiol. Rev.* **2007**, *20*, 660.

[41] B. Hu, L.-P. Zeng, X.-L. Yang, X.-Y. Ge, W. Zhang, B. Li, J.-Z. Xie, X.-R. Shen, Y.-Z. Zhang, N. Wang, *PLoS Pathog.* **2017**, *13*, e1006698.

[42] R. L. Graham, E. F. Donaldson, R. S. Baric, *Nat. Rev. Microbiol.* **2013**, *11*, 836.

[43] Y. Yin, R. G. Wunderink, *Respirology* **2018**, *23*, 130.

[44] E. de Wit, N. van Doremalen, D. Falzarano, V. J. Munster, *Nat. Rev. Microbiol.* **2016**, *14*, 523.

[45] J. Gu, C. Korteweg, *Am. J. Pathol.* **2007**, *170*, 1136.

[46] Y. Ding, H. Wang, H. Shen, Z. Li, J. Geng, H. Han, J. Cai, X. Li, W. Kang, D. Weng, *J. Pathol.* **2003**, *200*, 282.

[47] J. M. Nicholls, L. L. Poon, K. C. Lee, W. F. Ng, S. T. Lai, C. Y. Leung, C. M. Chu, P. K. Hui, K. L. Mak, W. Lim, *Lancet* **2003**, *361*, 1773.

[48] A. M. Zaki, S. Van Boheemen, T. M. Bestebroer, A. D. Osterhaus, R. A. Fouchier, *N. Engl. J. Med.* **2012**, *367*, 1814.

[49] S. van Boheemen, M. de Graaf, C. Lauber, T. M. Bestebroer, V. S. Raj, A. M. Zaki, A. D. Osterhaus, B. L. Haagmans, A. E. Gorbalenya, E. J. Snijder, *mBio* **2012**, *3*, e00473.

[50] Y. M. Arabi, H. H. Balkhy, F. G. Hayden, A. Bouchama, T. Luke, J. K. Baillie, A. Al-Omari, A. H. Hajeer, M. Senga, M. R. Denison, *N. Engl. J. Med.* **2017**, *376*, 584.

[51] WHO, MERS Monthy Summary, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), World Health Organization, Geneva **2019**.

[52] J. F. Drexler, V. M. Corman, C. Drosten, *Antiviral Res.* **2014**, *101*, 45.

[53] Z. A. Memish, N. Mishra, K. J. Olival, S. F. Fagbo, V. Kapoor, J. H. Epstein, R. AlHakeem, A. Durosinloun, A. Al Asmari, A. Islam, *Emerging Infect. Dis.* **2013**, *19*, 1819.

[54] E. I. Azhar, S. A. El-Kafrawy, S. A. Farraj, A. M. Hassan, M. S. Al-Saeed, A. M. Hashem, T. A. Madani, *N. Engl. J. Med.* **2014**, *370*, 2499.

[55] C. B. Reusken, B. L. Haagmans, M. A. Müller, C. Gutierrez, G.-J. Godeke, B. Meyer, D. Muth, V. S. Raj, L. Smits-De Vries, V. M. Corman, *Lancet Infect. Dis.* **2013**, *13*, 859.

[56] J. C. Hunter, D. Nguyen, B. Aden, Z. Al Bandar, W. Al Dhaheri, K. A. Elkheir, A. Khudair, A. Al Mulla, F. El Saleh, H. Imambaccus, *Emerging Infect. Dis.* **2016**, *22*, 647.

[57] G. Chowell, F. Abdirizak, S. Lee, J. Lee, E. Jung, H. Nishiura, C. Viboud, *BMC Med.* **2015**, *13*, 210.

[58] A. Assiri, J. A. Al-Tawfiq, A. A. Al-Rabeeah, F. A. Al-Rabiah, S. Al-Hajjar, A. Al-Barrak, H. Flemban, W. N. Al-Nassir, H. H. Balkhy, R. F. Al-Hakeem, *Lancet Infect. Dis.* **2013**, *13*, 752.

[59] M. Saad, A. S. Omrani, K. Baig, A. Bahloul, F. Elzein, M. A. Matin, M. A. Selim, M. Al Mutairi, D. Al Nakhli, A. Y. Al Aidaroos, *Int. J. Infect. Dis.* **2014**, *29*, 301.

[60] A. Zumla, D. S. Hui, S. Perlman, *Lancet* **2015**, *386*, 995.

[61] Y. M. Arabi, A. A. Arifi, H. H. Balkhy, H. Najm, A. S. Aldawood, A. Ghabashi, H. Hawa, A. Alothman, A. Khaldi, B. Al Raiy, *Ann. Intern. Med.* **2014**, *160*, 389.

[62] D. L. Ng, F. Al Hosani, M. K. Keating, S. I. Gerber, T. L. Jones, M. G. Metcalfe, S. Tong, Y. Tao, N. N. Alami, L. M. Haynes, *Am. J. Pathol.* **2016**, *186*, 652.

[63] K. O. Alsaad, A. H. Hajeer, M. Al Balwi, M. Al Moaiqel, N. Al Oudah, A. Al Ajlan, S. AlJohani, S. Alsolamy, G. E. Gmati, H. Balkhy, *Histopathology* **2018**, *72*, 516.

[64] R.-h. Cha, S. H. Yang, K. C. Moon, J.-S. Joh, J. Y. Lee, H.-S. Shin, D. K. Kim, Y. S. Kim, *J. Korean Med. Sci.* **2016**, *31*, 635.

[65] M.-L. Yeung, Y. Yao, L. Jia, J. F. Chan, K.-H. Chan, K.-F. Cheung, H. Chen, V. K. Poon, A. K. Tsang, K. K. To, M.-K. Yiu, J. L. L. Teng, H. Chu, J. Zhou, Q. Zhang, W. Deng, S. K. P. Lau, J. Y. N. Lau, P. C. Y. Woo, T.-M. Chan, S. Yung, B.-J. Zheng, D.-Y. Jin, P. W. Mathieson, C. Qin, K.-Y. Yuen, *Nat. Microbiol.* **2016**, *1*, 16004.

[66] W. Wang, J. Tang, F. Wei, *J. Med. Virol.* **2020**, *92*, 441.

[67] M. Roser, H. Ritchie, E. Ortiz-Ospina, J. Hasell, Coronavirus Disease (COVID-19), Our World in Data, **2020**.

[68] S. Garg, *Morb. Mortal. Wkly. Rep.* **2020**, *69*, 458.

[69] T. T.-Y. Lam, M. H.-H. Shum, H.-C. Zhu, Y.-G. Tong, X.-B. Ni, Y.-S. Liao, W. Wei, W. Y.-M. Cheung, W.-J. Li, L.-F. Li, G. M. Leung, E. C. Holmes, Y.-L. Hu, Y. Guan, *Nature* **2020**, *1*, https://doi.org/10.1038/s41586-020-2169-0.

[70] A. J. Turner, in *The Protective Arm of the Renin Angiotensin System (RAS)* (Eds: T. Unger, U. M. Steckelings, R. A. S. dos Santos), Academic Press, Boston, MA **2015**, pp. 185–189.

[71] M. K. S. Wong, in *Handbook of Hormones* (Eds: Y. Takei, H. Ando, K. Tsutsui), Academic Press, San Diego, CA **2016**, p. 253-e229-253.

[72] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, J. M. Penninger, *Nat. Med.* **2005**, *11*, 875.

[73] K. B. Brosnihan, A. A. Neves Liomar, C. Chappell Mark, *Hypertension* **2005**, *46*, 1097.

[74] M.-l. Huang, X. Li, Y. Meng, B. Xiao, Q. Ma, S.-s. Ying, P.-s. Wu, Z.-s. Zhang, *Clin. Exp. Pharmacol. Physiol.* **2010**, *37*, e1.

[75] C. I. Paules, H. D. Marston, A. S. Fauci, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 707.

[76] C. Tikellis, M. C. Thomas, *Int. J. Pept.* **2012**, *2012*, 256294.

[77] S. A. Lauer, K. H. Grantz, Q. Bi, F. K. Jones, Q. Zheng, H. R. Meredith, A. S. Azman, N. G. Reich, J. Lessler, *Ann. Intern. Med.* **2020**, *172*, 577.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

[78] J. A. Backer, D. Klinkenberg, J. Wallinga, *Eurosurveillance* **2020**, *25*, 2000062.

[79] N. M. Linton, T. Kobayashi, Y. Yang, K. Hayashi, A. R. Akhmetzhanov, S.-m. Jung, B. Yuan, R. Kinoshita, H. Nishiura, *J. Clin. Med.* **2020**, *9*, 538.

[80] A. S. Fauci, H. C. Lane, R. R. Redfield, *N. Engl. J. Med.* **2020**, *382*, 1268.

[81] J. Riou, C. L. Althaus, *Eurosurveillance* **2020**, *25*, 2000058.

[82] X. He, E. H. Y. Lau, P. Wu, X. Deng, J. Wang, X. Hao, Y. C. Lau, J. Y. Wong, Y. Guan, X. Tan, X. Mo, Y. Chen, B. Liao, W. Chen, F. Hu, Q. Zhang, M. Zhong, Y. Wu, L. Zhao, F. Zhang, B. J. Cowling, F. Li, G. M. Leung, *Nat. Med.* **2020**, *26*, 672.

[83] L. Zou, F. Ruan, M. Huang, L. Liang, H. Huang, Z. Hong, J. Yu, M. Kang, Y. Song, J. Xia, Q. Guo, T. Song, J. He, H.-L. Yen, M. Peiris, J. Wu, *N. Engl. J. Med.* **2020**, *382*, 1177.

[84] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel, G. Froeschl, C. Wallrauch, T. Zimmer, V. Thiel, C. Janke, W. Guggemos, M. Seilmaier, C. Drosten, P. Vollmar, K. Zwirglmaier, S. Zange, R. Wölfel, M. Hoelscher, *N. Engl. J. Med.* **2020**, *382*, 970.

[85] A. Bernheim, X. Mei, M. Huang, Y. Yang, Z. A. Fayad, N. Zhang, K. Diao, B. Lin, X. Zhu, K. Li, S. Li, H. Shan, A. Jacobi, M. Chung, *Radiology* **2020**, *295*, 200463.

[86] N. Petrosillo, G. Viceconte, O. Ergonul, G. Ippolito, E. Petersen, *Clin. Microbiol. Infect.* **2020**, *26*, 729.

[87] C. Menni, C. H. Sudre, C. J. Steves, S. Ourselin, T. D. Spector, T. D. Spector, *Lancet* **2020**, *395*, e107.

[88] J. Sun, W.-T. He, L. Wang, A. Lai, X. Ji, X. Zhai, G. Li, M. A. Suchard, J. Tian, J. Zhou, *Trends Mol. Med.* **2020**, *26*, 483.

[89] K. Ramphul, S. G. Mejias, *Cureus* **2020**, *12*, e7276.

[90] G. Kampf, D. Todt, S. Pfaender, E. Steinmann, *J. Hosp. Infect.* **2020**, *104*, 246.

[91] C. Ziegler, S. J. Allon, S. K. Nyquist, I. M. Mbano, V. N. Miao, C. N. Tzouanas, Y. Cao, A. S. Yousif, J. Bals, B. M. Hauser, J. Feldman, C. Muus, M. H. Wadsworth 2nd, S. W. Kazer, T. K. Hughes, B. Doran, G. J. Gatter, M. Vukovic, F. Taliaferro, B. E. Mead, *Cell* **2020**, *18*, 1016.

[92] H. Li, L. Liu, D. Zhang, J. Xu, H. Dai, N. Tang, X. Su, B. Cao, *Lancet* **2020**, *395*, 1517.

[93] A. Zaki, *Int. Soc. Infect. Dis. ProMED-mail* **2012**, http://www.promedmail.org/direct.php?id=20120920.1302733 (accessed: September 2020).

[94] D. K. Chu, L. L. Poon, M. M. Gomaa, M. M. Shehata, R. A. Perera, D. A. Zeid, A. S. El Rifay, L. Y. Siu, Y. Guan, R. J. Webby, *Emerging Infect. Dis.* **2014**, *20*, 1049.

[95] Z. Song, Y. Xu, L. Bao, L. Zhang, P. Yu, Y. Qu, H. Zhu, W. Zhao, Y. Han, C. Qin, *Viruses* **2019**, *11*, 59.

[96] A. Caldaria, C. Conforti, N. Di Meo, C. Dianzani, M. Jafferany, T. Lotti, I. Zalaudek, R. Giuffrida, *Dermatol. Ther.* **2020**, *33*, e13395

[97] P. Vijayanand, M. W. Wilkins, *Clin. Med.* **2004**, *4*, 152.

[98] C. Leung, W. Chiu, *Paediatr. Respir. Rev.* **2004**, *5*, 275.

[99] K. McIntosh, Severe acute respiratory syndrome (SARS), https://www.uptodate.com/contents/severe-acute-respiratory-syndrome-sars, (Accessed: August 2020).

[100] J. R. Hageman, *Pediatr. Ann.* **2020**, *49*, e99.

[101] D. K. W. Chu, Y. Pan, S. M. S. Cheng, K. P. Y. Hui, P. Krishnan, Y. Liu, D. Y. M. Ng, C. K. C. Wan, P. Yang, Q. Wang, M. Peiris, L. L. M. Poon, *Clin. Chem.* **2020**, *66*, 549.

[102] C. Tse, J. Capeau, *Ann. Biol. Clin.* **2003**, *61*, 279.

[103] W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, W. Tan, *JAMA, J. Am. Med. Assoc.* **2020**, *323*, 1843.

[104] Y. Y. Kong, C. H. Thay, T. C. Tin, S. Devi, *J. Virol. Methods* **2006**, *138*, 123.

[105] F. Osman, T. Olineka, E. Hodzic, D. Golino, A. Rowhani, *J. Virol. Methods* **2012**, *179*, 303.

[106] S. K. Vashist, *Diagnostics* **2020**, *10*, 202.

[107] M. J. Loeffelholz, Y.-W. Tang, *Emerging Microbes Infect.* **2020**, *9*, 747.

[108] P. Huang, T. Liu, L. Huang, H. Liu, M. Lei, W. Xu, X. Hu, J. Chen, B. Liu, *Radiology* **2020**, *295*, 22.

[109] G. Lippi, A.-M. Simundic, M. Plebani, *Clin. Chem. Lab. Med.* **2020**, *58*, 1070.

[110] L. E. Lamb, S. N. Bartolone, E. Ward, M. B. Chancellor, Rapid Detection of Novel Coronavirus (COVID19) by Reverse Transcription-Loop-Mediated Isothermal Amplification, https://doi.org/10.2139/ssrn.3539654 (accessed: February 2020).

[111] P. R. Sahoo, K. Sethy, S. Mohapatra, D. Panda, *Vet. World* **2016**, *9*, 465.

[112] T. Notomi, H. Okayama, H. Masubuchi, T. Yonekawa, K. Watanabe, N. Amino, T. Hase, *Nucleic Acids Res.* **2000**, *28*, e63.

[113] F. Zhang, O. O. Abudayyeh, J. S. Gootenberg, *A Protocol for Detection of COVID-19 Using CRISPR Diagnostics*, Broad Institute, MIT, Cambridge, MA **2020**.

[114] F. Pan, T. Ye, P. Sun, S. Gui, B. Liang, L. Li, D. Zheng, J. Wang, R. L. Hesketh, L. Yang, C. Zheng, *Radiology* **2020**, *295*, 200370.

[115] S. Henwood, *Clinical CT: Techniques and Practice*, Alden Press, Oxford **1999**.

[116] H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, Y. Fan, C. Zheng, *Lancet Infect. Dis.* **2020**, *20*, 425.

[117] W. Zhao, Z. Zhong, X. Xie, Q. Yu, J. Liu, *Am. J. Roentgenol.* **2020**, *214*, 1072.

[118] W. Yang, F. Yan, *Radiology* **2020**, *295*, 200702.

[119] T. Nguyen, D. Duong Bang, A. Wolff, *Micromachines* **2020**, *11*, 306.

[120] T. Yang, Y.-C. Wang, C.-F. Shen, C.-M. Cheng, *Diagnostics* **2020**, *10*, 165.

[121] P. Brangel, A. Sobarzo, C. Parolo, B. S. Miller, P. D. Howes, S. Gelkop, J. J. Lutwama, J. M. Dye, R. A. McKendry, L. Lobel, *ACS Nano* **2018**, *12*, 63.

[122] A. J. Jääskeläinen, E. M. Korhonen, E. Huhtamo, M. Lappalainen, O. Vapalahti, H. Kallio-Kokko, *J. Virol. Methods* **2019**, *263*, 68.

[123] G. Cabral-Miranda, A. R. Cardoso, L. C. Ferreira, M. G. F. Sales, M. F. Bachmann, *Biosens. Bioelectron.* **2018**, *113*, 101.

[124] Y. Chen, R. Ren, H. Pu, X. Guo, J. Chang, G. Zhou, S. Mao, M. Kron, J. Chen, *Sci. Rep.* **2017**, *7*, 10974.

[125] S. Hassanpour, B. Baradaran, M. Hejazi, M. Hasanzadeh, A. Mokhtarzadeh, M. de la Guardia, *TrAC, Trends Anal. Chem.* **2018**, *98*, 201.

[126] J. M. Yang, K. R. Kim, C. S. Kim, *Biotechnol. Bioprocess Eng.* **2018**, *23*, 371.

[127] A. Mokhtarzadeh, R. Eivazzadeh-Keihan, P. Pashazadeh, M. Hejazi, N. Gharaatifar, M. Hasanzadeh, B. Baradaran, M. de la Guardia, *TrAC, Trends Anal. Chem.* **2017**, *97*, 445.

[128] M. Soler, C. S. Huertas, L. M. Lechuga, *Expert Rev. Mol. Diagn.* **2019**, *19*, 71.

[129] S. M. Yoo, S. Y. Lee, *Trends Biotechnol.* **2016**, *34*, 7.

[130] J. Fung, S. K. Lau, P. C. Woo, *MERS Coronavirus*, Springer, New York **2020**, pp. 89–97.

[131] World Health Organization, Laboratory Testing for Coronavirus Disease 2019 (COVID-19) in Suspected Human Cases: Interim Guidance, 2 March 2020, World Health Organization, Geneva **2020**.

[132] Z. Li, Y. Wang, J. Wang, Z. Tang, J. G. Pounds, Y. Lin, *Anal. Chem.* **2010**, *82*, 7008.

[133] N. Wiriyachaiporn, W. Maneeprakorn, C. Apiwat, T. Dharakul, *Microchim. Acta* **2015**, *182*, 85.

[134] S. Y. Xiao, Y. Wu, H. Liu, *J. Med. Virol.* **2020**, *92*, 464.

[135] P. C. Woo, S. K. Lau, B. H. Wong, H.-w. Tsoi, A. M. Fung, R. Y. Kao, K.-h. Chan, J. M. Peiris, K.-y. Yuen, *J. Clin. Microbiol.* **2005**, *43*, 3054.

[136] Y.-W. Tang, J. E. Schmitz, D. H. Persing, C. W. Stratton, *J. Clin. Microbiol.* **2020**, *58*, e00512.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

[137] A. H. Bruning, M. M. Leeflang, J. M. Vos, R. Spijker, M. D. de Jong, K. C. Wolthers, D. Pajkrt, *Clin. Infect. Dis.* **2017**, *65*, 1026.

[138] IgM/IgG/IgA Antibody Detection Kit (Indirect ELISA), https://www.raybiotech.com/coronavirus-research-products-covid-19/ (accessed: September 2020).

[139] LEADGENE® SARS/SARS-CoV-2 Antigen Rapid Test, http://www.leadgenebio.com/web/product/product_in.jsp?pd_no=PD1587366405796&lang=en (accessed: September 2020).

[140] EDI™ Novel Coronavirus COVID-19 ELISA Kits, http://www.epitopediagnostics.com/covid-19-elisa (accessed: September 2020).

[141] SARS-CoV-2 Antigens and Antibodies, https://www.creative-diagnostics.com/news-sars-cov-2-antigens-and-antibodies-79.htm (accessed: September 2020).

[142] 2019-nCoV IgG/IgM Rapid Test, http://en.dynamiker.com/index/index/pro_info/aid/606.html (accessed: September 2020).

[143] ichroma COVID-19 Ab, http://www.boditech.co.kr/eng/board/news/board_view.asp?num=30168 (accessed: September 2020).

[144] COVID-19 IgG/IgM Rapid Test Development Kit, https://www.mybiosource.com/covid-19-assay-kits/covid-19-coronavirus/2563888 (accessed: September 2020).

[145] What is SONA's coronavirus test?, https://sonanano.com/covid-19/ (accessed: September 2020).

[146] COVID-19 IgG/IgM Test, https://www.btnx.com/Product?id=2008 (accessed: September 2020).

[147] A kit for the qualitative test of SARS-CoV-2 antibody by immunochromatography, http://sugentech.com/products/products-view.php?ct=7&target=32 (accessed: September 2020).

[148] Rapid point-of-care testing for the virus that causes COVID-19, https://www.mesabiotech.com/coronavirus (accessed: April 2020).

[149] GenMark Responds to the SARS-CoV-2 Outbreak, https://www.genmarkdx.com/solutions/panels/eplex-panels/eplex-sars-cov-2-test/ (accessed: April 2020).

[150] Aytu BioScience COVID-19 IgG/IgM Rapid Test, https://aytubio.com/covid-19/#covid-19 (accessed: September 2020).

[151] J. P. Broughton, X. Deng, G. Yu, C. L. Fasching, V. Servellita, J. Singh, X. Miao, J. A. Streithorst, A. Granados, A. Sotomayor-Gonzalez, K. Zorn, A. Gopez, E. Hsu, W. Gu, S. Miller, C.-Y. Pan, H. Guevara, D. A. Wadford, J. S. Chen, C. Y. Chiu, *Nat. Biotechnol.* **2020**, *38*, 870.

[152] Bosch rapid test for COVID-19, https://www.bosch.com/stories/vivalytic-rapid-test-for-covid-19/ (accessed: September 2020).

[153] Sherlock™ CRISPR SARS-CoV-2, https://sherlock.bio/crispr-sars-cov-2/ (accessed: September 2020).

[154] Synthetic SARS-CoV-2 RNA sequences, https://caspr.bio/technology.html (accessed: September 2020).

[155] Xpert® Xpress SARS-CoV-2, https://www.cepheid.com/coronavirus (accessed: 2020).

[156] ID NOW: The Forefront of COVID-19 Testing, https://www.abbott.com/IDNOW.html?CID=OUS_OK (accessed: 2020).

[157] Smart Detect™ SARS-CoV-2 rRT-PCR Kit, https://inbios.com/smart-detecttm-sars-cov-2-rrt-pcr-kit/ (accessed: 2020).

[158] Bosphore Novel Coronavirus (2019-nCoV) Detection Kit, http://www.anatoliageneworks.com/en/kitler.asp?id=360&baslik=Bosphore%20Novel%20Coronavirus%20(2019-nCoV)%20Detection%20Kit&bas=Bosphore%20Novel%20Coronavirus%20(2019-nCoV)%20Detection%20Kit (accessed: September 2020).

[159] WHO, Clinical Management of Severe Acute Respiratory Infection when COVID-19 is Suspected: Interim Guidance, World Health Organization, Geneva **2020**.

[160] R. Augustine, A. Hasan, S. Das, R. Ahmed, Y. Mori, T. Notomi, B. D. Kevadiya, A. S. Thakor, *Biology* **2020**, *9*, 182.

[161] Z. Li, Y. Yi, X. Luo, N. Xiong, Y. Liu, S. Li, R. Sun, Y. Wang, *J. Med. Virol.* **2020**, *92*, 1518.

[162] M. Francone, F. Iafrate, G. M. Masci, S. Coco, F. Cilia, L. Manganaro, V. Panebianco, C. Andreoli, M. C. Colaiacomo, M. A. Zingaropoli, M. R. Ciardi, C. M. Mastroianni, F. Pugliese, F. Alessandri, O. Turriziani, P. Ricci, C. Catalano, *Eur. Radiol.* **2020**, *30*, 6808.

[163] L. Shang, J. Zhao, Y. Hu, R. Du, B. Cao, *Lancet* **2020**, *395*, 683.

[164] L. J. Stockman, R. Bellamy, P. Garner, *PLoS Med.* **2006**, *3*, e343.

[165] Y. M. Arabi, Y. Mandourah, F. Al-Hameed, A. A. Sindi, G. A. Almekhlafi, M. A. Hussein, J. Jose, R. Pinto, A. Al-Omari, A. Kharaba, A. Almotairi, K. Al Khatib, B. Alraddadi, S. Shalhoub, A. Abdulmomen, I. Qushmaq, A. Mady, O. Solaiman, A. M. Al-Aithan, R. Al-Raddadi, A. Ragab, H. H. Balkhy, A. Al Harthy, A. M. Deeb, H. Al Mutairi, A. Al-Dawood, L. Merson, F. G. Hayden, R. A. Fowler, Saudi Critical Care Trial Group, *Am. J. Respir. Crit. Care Med.* **2018**, *197*, 757.

[166] R. A. Siemieniuk, M. O. Meade, P. Alonso-Coello, M. Briel, N. Evaniew, M. Prasad, P. E. Alexander, Y. Fei, P. O. Vandvik, M. Loeb, G. H. Guyatt, *Ann. Intern. Med.* **2015**, *163*, 519.

[167] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, *Lancet* **2020**, *395*, 1054.

[168] Y. Wang, W. Jiang, Q. He, C. Wang, B. Wang, P. Zhou, N. Dong, Q. Tong, medRxiv 2020.03.06.20032342; https://doi.org/10.1101/2020.03.06.20032342, **2020**.

[169] O. Mitja, B. Clotet, *Lancet* **2020**, *8*, e639.

[170] Y. R. Guo, Q. D. Cao, Z. S. Hong, Y. Y. Tan, S. D. Chen, H. J. Jin, K. S. Tan, D. Y. Wang, Y. Yan, *Mil. Med. Res.* **2020**, *7*, 11.

[171] J. Lim, S. Jeon, H. Y. Shin, M. J. Kim, Y. M. Seong, W. J. Lee, K. W. Choe, Y. M. Kang, B. Lee, S. J. Park, *J. Korean Med. Sci.* **2020**, *35*, e79.

[172] B. Cao, Y. Wang, D. Wen, W. Liu, J. Waang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, et al., *New Engl. J. Med.* **2020**, *382*, 1787.

[173] X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, E. Dong, C. Song, S. Zhan, R. Lu, H. Li, W. Tan, D. Liu, *Clin. Infect. Dis.* **2020**, *71*, 732.

[174] M. G. S. Borba, F. d. A. Val, V. S. Sampaio, M. A. A. Alexandre, G. C. Melo, M. Brito, medRxiv *JAMA Netw Open* **2020**, *3*, e208857.

[175] M. Mahevas, V.-T. Tran, M. Roumier, A. Chabrol, R. Paule, C. Guillaud, S. Gallien, R. Lepeule, T.-A. Szwebel, X. Lescure, F. Schlemmer, M. Matigon, M. Khellaf, E. Cricks, B. Terrier, *BMJ* **2020**, *369*, m1844.

[176] W. Tang, Z. Cao, M. Han, Z. Wang, J. Chen, W. Sun, Y. Wu, W. Xiao, S. Liu, E. Chen, W. Chen, X. Wang, J. Yang, J. Lin, Q. Zhao, Y. Yan, *BMJ* **2020**, *369*, m1849.

[177] P. Gautret, J.-C. Lagier, P. Parola, V. T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giodanengo, V. E. Vieira, H. T. Dupont, S. Honore, P. Colson, *Int. J. Antimicrob. Agents* **2020**, *56*, 105949.

[178] J. M. Molina, C. Delaugerre, J. Le Goff, B. Mela-Lima, D. Ponscarme, L. Goldwirt, N. de Castro, *Med. Mal. Infect.* **2020**, *50*, 384.

[179] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castanaga, T. Feldt, G. Green, M. L. Green, F. Lescure, *New Engl. J. Med.* **2020**, *382*, 2327.

[180] C. Chen, Y. Zhang, J. Huang, P. Yin, Z. Cheng, J. Wu, S. Chen, Y. Zhang, B. Chen, M. Lu, Y. Luo, L. Ju, J. Zhang, X. Wang, *medRxiv*, https://doi.org/10.1101/2020.03.17.20037432, **2020**.

[181] T. P. Sheahan, A. C. Sims, S. Zhou, R. L. Graham, A. J. Pruijssers, M. L. Agostini, S. R. Leist, A. Schafer, K. H. Dinnon 3rd, L. J. Stevens, J. D. Chappell, X. Lu, T. M. Hughes, A. S. George, C. S. Hill, S. A. Montgomery, A. J. Brown, G. R. Bluemling, M. G. Natchus, M. Saindane, A. A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N. J. Thornburg, R. Swanstrom, M. R. Denison, R. S. Baric, *Sci. Transl. Med.* **2020**, *12*, eabb5883.

[182] B. Boras, R. Jones, B. Anson, D. Areson, L. Aschenbrenner, M. Bakowski, N. Beutler, J. Binder, E. Chen, *bioRxiv* **2020**.

[183] SLV213: A Potential Treatment for COVID-19. Selva Therapeutics, https://selvarx.com/selva/, (accessed: September 2020).

[184] Y. Cheng, R. Wong, Y. O. Y. Soo, W. S. Wong, C. K. Lee, M. H. L. Ng, P. Chan, K. C. Wong, C. B. Leung, G. Cheng, *Eur. J. Clin. Microbiol. Infect. Dis.* **2005**, *24*, 44.

[185] I. F. Hung, K. K. To, C. K. Lee, K. L. Lee, K. Chan, W. W. Yan, R. Liu, C. L. Watt, W. M. Chan, K. Y. Lai, C. K. Koo, T. Buckley, F. L. Chow, K. K. Wong, H. S. Chan, C. K. Ching, B. S. Tang, C. C. Lau, I. W. Li, S. H. Liu, K. H. Chan, C. K. Lin, K. Y. Yuen, *Clin. Infect. Dis.* **2011**, *52*, 447.

[186] Y. M. Arabi, A. H. Hajeer, T. Luke, K. Raviprakash, H. Balkhy, S. Johani, A. Al-Dawood, S. Al-Qahtani, A. Al-Omari, F. Al-Hameed, F. G. Hayden, R. Fowler, A. Bouchama, N. Shindo, K. Al-Khairy, G. Carson, Y. Taha, M. Sadat, M. Alahmadi, *Emerging Infect. Dis.* **2016**, *22*, 1554.

[187] C. Shen, Z. Wang, F. Zhao, Y. Yang, J. Li, J. Yuan, F. Wang, D. Li, M. Yang, L. Xing, J. Wei, H. Xiao, Y. Yang, J. Qu, L. Qing, L. Chen, Z. Xu, L. Peng, Y. Li, H. Zheng, F. Chen, K. Huang, Y. Jiang, D. Liu, Z. Zhang, Y. Liu, L. Liu, *J. Am. Med. Assoc.* **2020**, *323*, 1582.

[188] K. Duan, B. Liu, C. Li, H. Zhang, T. Yu, J. Qu, M. Zhou, L. Chen, S. Meng, Y. Hu, C. Peng, M. Yuan, J. Huang, Z. Wang, J. Yu, X. Gao, D. Wang, X. Yu, L. Li, J. Zhang, X. Wu, B. Li, Y. Xu, W. Chen, Y. Peng, Y. Hu, L. Lin, X. Liu, S. Huang, Z. Zhou, L. Zhang, Y. Wang, Z. Zhang, K. Deng, Z. Xia, Q. Gong, W. Zhang, X. Zheng, Y. Liu, H. Yang, D. Zhou, D. Yu, J. Hou, Z. Shi, S. Chen, Z. Chen, X. Zhang, X. Yang, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 9490.

[189] H. Bisht, A. Roberts, L. Vogel, K. Subbarao, B. Moss, *Virology* **2005**, *334*, 160.

[190] Y. W. Kam, F. Kien, A. Roberts, Y. C. Cheung, E. W. Lamirande, L. Vogel, S. L. Chu, J. Tse, J. Guarner, S. R. Zaki, K. Subbarao, M. Peiris, B. Nal, R. Altmeyer, *Vaccine* **2007**, *25*, 729.

[191] S. U. Kapadia, J. K. Rose, E. Lamirande, L. Vogel, K. Subbarao, A. Roberts, *Virology* **2005**, *340*, 174.

[192] Z. Y. Yang, W. P. Kong, Y. Huang, A. Roberts, B. R. Murphy, K. Subbarao, G. J. Nabel, *Nature* **2004**, *428*, 561.

[193] N. Pardi, M. J. Hogan, F. W. Porter, D. Weissman, *Nat. Rev. Drug Discovery* **2018**, *17*, 261.

[194] X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Mu, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qian, *Nat. Commun.* **2020**, *11*, 1620.

[195] A. Roldao, M. C. Mellado, L. R. Castilho, M. J. Carrondo, P. M. Alves, *Expert Rev. Vaccines* **2010**, *9*, 1149.

[196] M. E. Saad, R. A. Elsalamony, *Int. J. Cancer Biomed. Res.* **2020**, *5*, 14.

[197] A. Siani, *Prev. Med.* **2019**, *121*, 99.

[198] C. Ma, Z. An, L. Hao, K. L. Cairns, Y. Zhang, J. Ma, L. Cao, L. Wen, W. Xu, X. Liang, W. Yang, H. Luo, *J. Infect. Dis.* **2011**, *204*, S447.

Zhina Hadisi is a Ph.D. student in the Department of Mechanical Engineering at the University of Victoria. Her doctoral research focuses on developing and characterizing smart dressings for the detection and identification of bacteria causing infection in wounds. She has a strong research background in cell culture, bacterial tests, and in vivo studies.

Tavia Walsh is a biomedical engineer, specializing in next-generation wound care strategies using bioactive sutures and thread-based biosensors. She obtained her B.A.Sc. in Electrical Engineering from the University of British Columbia, and her M.A.Sc. in Mechanical Engineering from the University of Victoria.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
THERAPEUTICS**

www.advtherap.com

Mohsen Akbari is a bioengineer and an associate professor in the Department of Mechanical Engineering at the University of Victoria, Canada. Dr. Akbari directs the Laboratory for Innovation in Microengineering (LIME). He is particularly interested in combining the microengineering techniques with cellular biology to develop translational solutions for current grand challenges in health.