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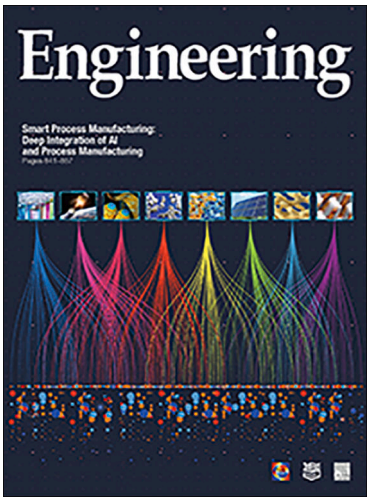

Editorial

Editorial for the Special Issue on COVID-19

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Editorial for the Special Issue on COVID-19

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Coronavirus disease 2019 (COVID-19) is caused by a positive-stranded RNA virus called severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus. It has rapidly spread to every corner of the globe, with 213 countries and territories infected in mid-April, due to its unprecedented capability of human-to-human transmission. Adverse outcomes of COVID-19 are manifested by lung disease associated with multi-organ dysfunction/failure, raising serious concerns, widespread apprehension, and individual panic and anxiety. While COVID-19 has been brought under effective control in China and some European countries such as Italy, Spain, and Germany, the pandemic remains a grim and complex threat to many other nations with its destructive power against global health, economies, and society. As of the end of September 2020, the reported number of COVID-19 patients is over seven million in the United States alone, which leads the world in number of infections and is followed by India, Brazil, and so forth. Even more concerning is the worsening trend that follows the ebb of the first COVID-19 tsunami: A second wave is on its way and may continue to spread and ravage the globe. In fact, some nations and regions have already witnessed the surge of a second wave. This situation is a true portrayal of a Chinese saying: “Hardly has one wave subsided when another rises”—meaning that one trouble follows another.

At present, we are facing the harsh plight of a lack of approved effective and standard treatment for COVID-19, even though there has been a rapid surge in both clinical and fundamental research in response to the COVID-19 outbreak. There is no doubt that sharing the lessons and warnings we have learned from the unanticipated COVID-19 outbreak, the knowledge and experience we have gained during our battle against the outbreak, and the scientific results and conclusions we have acquired through intensive research activities in the past months is opportune and desirable. This is one way in which we can

prepare for the upcoming COVID-19 second wave and minimize its devastating momentum. The editorial board of the journal *Engineering* thus decided to publish a special issue on COVID-19 in a timely manner.

This special issue aims to provide an opportunity for clinicians and scientists to bring forward new thoughts and ideas, discuss existing problems and questions, exchange views and opinions, and present current state-of-the-art findings on COVID-19 from both basic and clinical research. The contributions in this issue were carefully selected and rigorously peer-reviewed in order to maintain the high standards of this journal. The goal of this issue is to update our understanding of COVID-19 and its treatment from different angles covering five areas of COVID-19 research: clinical trials on drug treatment of COVID-19, alternative approaches for COVID-19 therapy, screening of an infected population, prevention of COVID-19 outbreak and spread, molecule-level attributes of the aggressive invasion of SARS-CoV-2 into human cells, and ethical and cultural considerations of COVID-19 management, as summarized below.

A primary and effective strategy for preventing SARS-CoV-2 dissemination has been emergency policymaking and the reinforcing of lockdown measures, including city closure, social isolation, economic lockdown, and individual quarantine. However, while the main therapies being used to treat the disease are antiviral drugs, chloroquine/hydroxychloroquine, and respiratory therapy in conjunction with life support, no therapeutic drugs or any other means have been validated as yet through large-scale studies to have significant efficacy in the clinical treatment of COVID-19 patients. Clearly, specifically designed randomized clinical trials are urgently needed to determine the most appropriate evidence-based treatment modality.

In this special issue, Boli Zhang contributes an article on the development of a core outcome set (COS) for clinical trials on COVID-19 (COS-COVID), in order to tackle the long-existing problematic practice of using non-standardized (i.e., inconsistent, nonstandard, irrational, and inessential) outcomes in clinical studies testing the efficacy and safety of medical interventions. The COS-COVID is expected to provide standardized, reliable, and practical outcome sets for evaluating the evidence-based treatment and management of COVID-19 patients, as well as guidelines for the more rational design of future clinical trials on this topic. The COS-COVID can be used not only in clinical trials, but also in systematic reviews/meta-analyses, guidelines, and other research on evidence evaluation and decision-making for COVID-19. When evaluating the integration of traditional Chinese medicine with Western medicine for treating COVID-19 patients, a gold index is to control patient symptoms from mild to severe.

Lei Liu and Wu Zhong present the findings from an open-label nonrandomized control study on the experimental treatment of COVID-19 with Favipiravir, a novel RNA-dependent RNA polymerase inhibitor with broad antiviral activities for the treatment of influenza and Ebola virus. Their group found that oral Favipiravir plus interferon (IFN)-α aerosol inhalation offered significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance. These results are essentially consistent with several recently published case studies and clinical trials.

In addition, a randomized, double-blinded controlled trial protocol conducted by Baofeng Yang's group for testing the efficacy and safety of Triazavirin treatment of COVID-19 is presented. These scholars found that the combination of Triazavirin and standard therapy is not associated with a statistically significant overall improvement of the clinical outcomes relative to a placebo. However, the percentage of patients showing clinical improvement with Triazavirin treatment was twice as high as that with a placebo, and the median time to clinical improvement was five days shorter with Triazavirin than with a placebo. In addition, patients with Triazavirin treatment received less frequent concomitant therapies for respiratory, cardiac, renal, hepatic, or coagulation supports. This work represents the first demonstration of the potential of Triazavirin for treating COVID-19.

A fascinating story in the battle against the COVID-19 outbreak concerns the amazing therapeutic efficacy of the Chinese herbal formula (CHF). Here, Liang Liu presents his finding on the potential uses and therapeutic mechanisms of CHFs from the reported literature and of patent drugs, the scientific bases for their efficacy in treating COVID-19, and the targeting mechanisms of CHFs on SARS-CoV-2. He also proposes an invaluable perspective on validating the therapeutic efficacy of CHFs in order to better elucidate their scientific foundations via multiple high-tech technologies, and promote the widespread understanding and acceptance of CHFs as an alternative medication for COVID-19.

The lack of an effective drug treatment for COVID-19 has prompted clinicians and scientists to consider alternative means for tackling the public health emergency. Boosting the immune function of patients and healthy subjects is an undoubted key to achieving the cure and prevention of diseases, particularly contagious ones such as COVID-19. Immunization—a key component of primary healthcare and an indisputable human right—saves 2–3 million lives every year. Vaccinations prevent

more than 20 life-threatening diseases, including infectious-disease outbreaks, by working with the natural defenses of the human body to build protection; thus, they underpin global health security and will be a vital tool in the battle against COVID-19. The development of effective vaccines is a top priority and a long-term solution to COVID-19. According to the World Health Organization, more than 100 candidate COVID-19 vaccines are presently under research and development worldwide in a race against time to accelerate the development of new treatments and vaccines, with China leading the way. *The Lancet* recently released the results from the phase I and II clinical trials of the first COVID-19 vaccine—a study led by Wei Chen from the Beijing Institute of Biotechnology. A single dose of this vaccine is safe and effective in generating SARS-CoV-2-specific antibodies in 14 days of infection in participants. These results represent an important milestone in our battle against COVID-19. Even more promising is that the phase II trial adds further evidence on safety and immunogenicity in a large population, prompting the phase III trials that are already underway. China has pledged that its COVID-19 vaccine will be made a global public good when it becomes available. In this special issue, Wei Chen shares her exciting, inspiring vaccine story and discusses the challenges and struggles associated with vaccine development. Major challenges include issues related to vaccine safety, efficacy, human challenge trials, and production capacity, which are not only scientific and technological constraints, but also ethical, economic, and public considerations.

In its most severe form, COVID-19 can lead to life-threatening pneumonia and acute respiratory distress syndrome (ARDS). Although the way in which COVID-19 leads to lethal lung injury is still being elucidated, the term "cytokine storm" (also known as "immune storm") has become synonymous for its pathophysiological mechanism, both in scientific publications and in the media, even though the linkage of a cytokine storm to COVID-19 remains to be verified. A cytokine storm is a hyperactive immune response characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators, which work together to cause lung injury. Widespread acceptance of cytokine storm as a mechanism for the fatal outcome of COVID-19 has motivated the application of potent immunomodulatory therapies to the clinical treatment of the syndrome. Here, Lanjuan Li presents her view and comments on the feasibility and promise of an artificial-liver blood-purification system as a cytokine-storm-targeted rescue therapy for the treatment of severely and critically ill COVID-19 patients exhibiting cytokine storm and rapid disease progression. She also proposes two directions to promote renovative practice: multicenter clinical studies to validate the application of artificial-liver blood-purification systems with confirmed ability to clear pro-inflammatory cytokines; and in-depth investigations on the key intracellular signaling pathways and immune cell types involved in cytokine storm onset in COVID-19.

It has been well articulated that the gut microbiota plays an important role in influencing lung diseases; in turn, respiratory virus infection can cause perturbations in the gut microbiota. Intriguingly, it was recently reported that SARS-CoV-2 RNA was found in the feces of infected patients. Gut microbiota diversity decreases in old age, and COVID-19 is fatal mainly in elderly patients. These findings all point to a role of the gut microbiota in controlling COVID-19, implying that improving the gut microbiota profile could be an alternative strategy for the disease. Indeed, in this special issue, Lanjuan Li provides a piece of strong evidence for the regulation of intestinal flora as a potential alternative strategy for the clinical treatment of COVID-19. Li's group conducted a clinical study and identified ten predominant intestinal flora as potential therapeutic targets and diagnostic biomarkers for COVID-19. They further established the intestinal *Enterococcu*/Enterobacteriaceae strain as a rapid nonintrusive early-warning signal for the diagnosis of COVID-19 and the death of critically ill patients. These findings should greatly boost the development of manipulating the gut microbiota profile for COVID-19 therapy. Furthermore, they are consistent with recent documentation on the beneficial effects of specific bacterial formulations on the clinical condition of patients who test positive for SARS-CoV-2 infection.

As another alternative therapeutic approach for COVID-19, mesenchymal stromal/stem cell (MSC) therapy has demonstrated initial promise in the treatment of ARDS, inflammation, and sepsis, which are among the leading causes of mortality in COVID-19 patients. This therapy has been shown to reduce the expression of pro-inflammatory cytokines and improve the repair of damaged tissues in COVID-19 patients by protecting alveolar epithelial cells, reclaiming the pulmonary microenvironment, preventing pulmonary fibrosis, and curing lung dysfunction. On this topic, Lanjuan Li presents some interesting results in a clinical study conducted by her team examining the efficacy of MSCs in treating ARDS induced by epidemic influenza A (H7N9) infection. Their data on H7N9 suggest the possibility of using MSC-based therapy as a promising alternative strategy for treating COVID-19 based on the following arguments. First, H7N9 and COVID-19 share similar complications (e.g., ARDS and lung failure) and corresponding multi-organ dysfunction. Second, H7N9-ARDS and

COVID-19 have similar symptoms, including fever, cough, shortness of breath, sputum, and dyspnea. Third, MSCs reduce the secretion of inflammatory factors, thereby suppressing cytokine storm through their immunomodulatory capacity, which constitutes a common signaling mechanism for suppressing a lethal event induced by influenza A and coronaviruses. This point is supported by Yi Zhang, who shares his views and comments on MSCs as a therapeutic option for COVID-19. Because of the wide spread of COVID-19, numerous clinical studies have been conducted to examine the effects of MSCs in COVID-19 patients.

The risk of severe COVID-19 infection is more common in those with high blood pressure, diabetes, or obesity, which represents a major challenge to the clinical treatment of COVID-19 patients. Jiao Guo addresses the importance of optimal management of the metabolic hemostasis of glucose and lipids to ensure better clinical outcomes in COVID-19 patients with diabetes, based on the results from a retrospective study her group conducted on the clinical characteristics and outcomes of type 2 diabetes patients infected with COVID-19. This study provides the first direct evidence supporting the high frequency of coexistence of type 2 diabetes and hypertension, coronary heart disease, and chronic renal disease in patients with COVID-19, and the higher level of severity in COVID-19 patients with metabolic comorbidities relative to control subjects without diabetes.

COVID-19 is highly contagious and requires early detection, isolation, and treatment. The importance of screening a population infected by SARS-CoV-2 to provide early diagnosis of COVID-19 for timely intervention and to stem the spread of the virus is far beyond words: Global endeavors to fight the Covid-19 pandemic have heavily relied on accurate, fast, and frequent tests for the coronavirus SARS-CoV-2. The prevalence of the disease requires mass or large-scale, high-throughput screening and testing. Here, Hongbing Shen's team reports on the development of a modified susceptible–exposed–infected–removed transmission dynamics model to unravel the unexpected lower magnitude and faster resolution of the COVID-19 epidemic in Wuhan. This unique model provides an invaluable tool and measure for predicting, preventing, and controlling current and future epidemic events.

Lanjuan Li describes a multicenter case study conducted by her research team to establish an early screening model for distinguishing COVID-19 from influenza A viral pneumonia and healthy cases with pulmonary computed tomography (CT) images using deep learning techniques. The remarkable overall accuracy rate (86.7%) suggests the use of deep learning models for the effective early screening of COVID-19 patients as a supplementary diagnostic tool.

Jing Cheng's team has developed a high-throughput, multi-index isothermal amplification platform (RTisochipTM-W system) for the rapid simultaneous detection of SARS-CoV-2. The platform is capable of identifying 19 different types of common respiratory viruses, including SARS-CoV-2, in a single test and presents the advantages of a short turnaround time, flexible throughput, minimum manual operations, and a high sensitivity that is comparable to that of conventional reverse-transcription polymerase chain reaction (RT-PCR). This platform provides a powerful and practical tool for the diagnosis and screening of SARS-CoV-2 and other respiratory viruses.

The spread and ravagement of SARS-CoV-2 has been primarily ascribed to its rapid radial transmission; vertical transmission of this virus remains controversial, although cases of transplacental transmission are increasingly being reported. The work presented in this special issue by Jie Qiao supports the potential risk of embryo infection during embryo transfer. Qiao's team analyzed the expression patterns of angiotensin-converting enzyme 2 (*ACE2*) and transmembrane protease serine 2 (*TMPRSS2*) in perimplantation embryos and the early maternal–fetal interface based on single-cell transcription data available in the literature, and found abundant co-expression of *ACE2* and *TMPRSS2* in Day 6 trophectoderm (TE) cells of perimplantation embryo and significant gender-difference of expression. They conclude that there is a possibility of vertical transmission in perimplantation embryo development and early pregnancy, arousing serious concern regarding this issue. Their findings raise the alarm for necessary measures to be taken to protect SARS-CoV-2-infected women who are pregnant or preparing for pregnancy.

Quarantine measures including citywide isolation, economic shutdown, and social activity lockdown are by far the most effective ways to contain the spread of SARS-CoV-2. Another layer of protection to keep individuals from infection involves wearing a mask and maintaining social distancing, as the highly virulent and pathogenic COVID-19 infection is primarily transmitted by breathing infected droplets or coming into contact with infected droplets.

Wearing masks is a basic and indispensable means of personal protection from inhaling or contacting virus-infected droplets; however, there is a huge demand-supply gap of masks in almost all countries and regions, which was present even

before the outbreak of the epidemic. In this regard, extending the serviceable lifetime of one-time masks for repeated use becomes desirable. In this issue, Jian-Feng Chen describes the development and validation of user-friendly practical technologies and methods for decontaminating used masks for multiple reuse, as well as a new method for the assessment of mask performance or the identification of faulty masks based on a penetrant inspection of fluorescent nanoparticles. This work provides a practical solution for mask shortage in emergency situations such as COVID-19, with feasible and economical procedures for the development and validation of reusable masks in response to a future epidemic outbreak.

Chen Wang led his team in the front lines in the fight against COVID-19 and innovatively created the temporary sub-medical facilities known as the "Fangcang Shelter Hospitals" (i.e., mobile cabin hospitals) that saved the lives of thousands of COVID-19 patients. Here, Wang presents an interesting study examining the impact of public holidays on the dissemination of COVID-19 by projecting the epidemic trend and epidemic trajectories with and without the public holiday policy, and using a compartment model to simulate the dynamic transmission of the virus in China. His results suggest that the extention of public holidays are a powerful approach to mitigate and hold back the spread of a new epidemic, and indicate the importance of implementing a public holiday policy in future pandemics.

While it is commonly accepted that bats are the original hosts of and a natural reservoir for SARS-CoV-2, how this virus got into the human body remains unclear. In theory, the virus could have evolved to its current pathogenic state through natural selection in a non-human host prior to relocation to humans; alternatively, a non-pathogenic version of the virus could have jumped from an animal host into a human, followed by mutation to its current pathogenic state within the human population. Nevertheless, the missing "patient zero" leaves scientists caught in the dilemma of dissecting these two possibilities. Here, Jiuhui Qu presents an interesting model: "Natural host—Environmental media—Human" for better investigation into the origin of COVID-19 and the pathway along which SARS-CoV-2 invades into the human body. This model introduces environmental media hosting SARS-CoV-2 (animal feces/water, soil, and food contaminated by animals' urine, saliva, feces, and secretions) into the pathway, and emphasizes its importance as a quasi-host to bridge the gap between the natural host (likely bat) and humans, thereby mediating the transition of SARS-CoV-2 from flying mammals to humans. This unique analysis enables source tracking of the origin of SARS-CoV-2 without identifying patient zero.

It is now clear that ACE2 receptors sitting on the cytoplasmic membrane are a gate for SARS-CoV-2 to invade into human cells (e.g., lung cells), and the keys to unlock this metaphorical latch are the tips of the mace-like spike proteins that project from SARS-CoV-2. Thereafter, SARS-CoV-2 hijacks the protein-making machinery of human cells to make copies of itself. In theory, the more *ACE2* a cell expresses, the more gates it opens; thus, the more susceptible it is to SARS-CoV-2 infection. The work presented by Jie Qiao, mentioned above, takes advantage of this mechanism by comparing the expression profiles of *ACE2* to uncover the potential risk of SARS-CoV-2 vertical transmission in perimplantation and early pregnancy.

From a narrow perspective, the COVID-19 epidemic/pandemic is primarily a medical issue. Yet from a broad point of view, this public health crisis profoundly impacts literally all aspects of society, including the economy, employment, the environment, public security, public activities, and even the daily-life activities of the population under threat. Failure to handle any of these issues could well worsen already difficult social situations. Precisely speaking, an event such as COVID-19 is a complex social problem that lies beyond just medical treatment and public health protection. He Liu raises an interesting point from a very different angle concerning COVID-19 prevention and control: the ethical issue. His article regards COVID-19 prevention and control work as an emergency engineering management system involving different groups of stakeholders including local decision-makers (local governments), medical scientists, health workers, and the public, according to their respective roles.

Each paper in this special issue has its own unique entry point into and perspective on the new coronavirus and its associated disease. Together, they highlight the current status of and advances in both basic and clinical research related to the global emergency of the pandemic. This compilation is an effort to bring together state-of-the-art research and perspectives in one place for better exchanges and discussion on the clinical and scientific issues related to COVID-19. In this way, we will be better equipped with new knowledge to repulse the next wave of the COVID-19 onslaught.

The COVID-19 epidemic is changing the international landscape. It will also have a profound impact on how people think and behave in the future. This epidemic has become the most prominent factor disturbing the world in the past six months, the present time, and probably the near future. However, we are far from fully understanding this virus and this disease, and it will be impossible for us to fully understand all infectious diseases in future. The question of future pandemics should not

be of concern only to the medical community; it should also concern all of society. We must consider the scientific and social problems we are facing, identify the responsibilities we should take on, and then transform these ideas into action.