Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

8 SARS-CoV-2 and the COVID-19 pandemic

The manuscript for this book was completed in March 2020 and submitted for publication. It consisted of seven chapters, a preface and an epilogue. At the same time, the United States and the world were struck by a virulent and highly contagious form of a coronavirus, referred to as the "novel" coronavirus or SARS-CoV-2. This virus resulted in a global pandemic referred to as COVID-19. Because of the unique and devastating nature of this health crisis, the book's publisher, Elsevier and I felt the need for this additional, late inserted chapter to offer a discussion of the virus, its epidemiology, clinical and bioscience, public health implications, and the immediate role and response AI has provided in the early stages of this pandemic. I also went back through the relevant topics in Chapters 4 through 7 and, as you will have noted, I added brief related comments on COVID-19 with references to the material in this new chapter.

Hopefully, by the time you read this chapter, the virus will have been eliminated or dramatically reduced through an effective vaccine or antiviral therapeutic agents. Furthermore, I apologize for any information in this chapter that will have been modified, updated or proven inaccurate at the time of your reading. The information I am providing now is either traditional, documented public health information from previous epidemics and pandemics or it is information and hypotheses being considered by experts as of September 2020.

8.1 Background

8.1.1 Definitions

An endemic level of disease can be defined as that level of observable disease found in a community and considered a baseline or expected level. Occasionally, the expected level of disease may rise, often suddenly, in a defined geographic area and is termed an "outbreak." If the rise in the cases are grouped in a specific place, it is considered a "cluster," but if they are broadly distributed, it is considered an "epidemic." Pandemic refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people [1].

Epidemics and pandemics occur when an infectious agent (e.g., a virus) is sufficiently virulent and contagious enough to be conveyed to a large number of susceptible hosts (e.g., humans). These conditions may result from:

- A recent increase in amount or virulence of the agent;
- The recent introduction of the agent into a setting where it has not been before;

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- An enhanced mode of transmission so that more susceptible persons are exposed;
- A change in the susceptibility of the host response to the agent; and/or
- Factors that increase host exposure or involve introduction through new portals of entry [2].

8.1.2 History of pandemics

8.1.2.1 Historical overview

Outbreaks of infectious disease have shaped the economic, political, and social aspects of human civilization, their effects often lasting for centuries. These outbreaks have defined some of the basic tenets of modern medicine with the development of the principles of epidemiology, prevention, immunization, and the field of public health. Throughout history, pandemic outbreaks have decimated societies, determined outcomes of wars, wiped out entire populations, yet paradoxically, they have ushered in new innovations, created and advanced sciences including medicine, immunology, genetics, public health as well as fields of economics and political science systems [3].

The best-known examples of recorded plagues are those referred to in religious writings starting with the Old Testament. The Athenian plague is an historically documented event that occurred in 430−26 BCE during the Peloponnesian War. This plague affected a majority of the inhabitants of the overcrowded city-state and claimed lives of more than 25% of the population [4]. Subsequent plagues over the centuries effected the Roman Empire (the Antonine plague [5]), the Justinian plague [6] and forward to 13th century and the Black Plague, a global outbreak of the bubonic plague that originated in China in 1334, arrived in Europe in 1347, and over the following 50 years it reduced the global population from 450 million to possibly below 300 million. Some estimates claim that the Black Death claimed up to 60% of lives in Europe at that time [7].

8.1.2.2 Recent history

Three influenza pandemics occurred at intervals of several decades during the 20th century, the most severe of which was the so-called “Spanish Flu” (caused by an A[H1N1] virus), estimated to have caused 20−50 million deaths in 1918−19. Milder pandemics occurred subsequently in 1957−58 (the “Asian Flu” caused by an A[H2N2] virus) and in 1968 (the “Hong Kong Flu” caused by an A[H3N2] virus), which were estimated to have caused one to 4 million deaths each.

Polio (classified as an epidemic) occurred in the United States from 1916 to its peak in 1952. Of the 57,628 reported cases, there were 3145 deaths. Dr. Jonas Salk developed a vaccine and in 1962, the average number of cases dropped to 910. The CDC Trusted Source reports that the United States has been polio-free since 1979 [8]. Unfortunately, there have been recent reports of new cases of polio developing in industrialized and developing countries [9].

First documented case of the human immunosuppressive virus (HIV) occurred in 1981. The pandemic first appeared to be a rare lung infection originating in Africa. Now it is known that it damages the body’s immune system and compromises its ability to fight off infections.

Acquired immune deficiency syndrome (AIDS) is the final stage of HIV and the 6th leading cause of death in the United States among people 25−44 years old. While no cure currently exists, treatment drugs have been developed and the number of deaths has fallen to 19% since 2005 [10].

The first influenza pandemic of the 21st century occurred in 2009−10 and was caused by an influenza A(H1N1) virus. This H1N1 pandemic was a reprise of the "Spanish flu" pandemic from 1918, but with far less devastating consequences. Suspected as a re-assortment of bird, swine, and human flu viruses, it was coined the "swine flu" [11]. For the first time, a pandemic vaccine was developed, produced and deployed in multiple countries during the first year of the pandemic. While most cases of pandemic H1N1 were mild, globally it is estimated that this 2009 pandemic caused between 100,000 and 400,000 deaths in the first year alone [12]. Other prominent epidemics and pandemics that occurred in the early 21st century included Ebola, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV), Nipah and henipa virus diseases, Zika, and others [13].

The first outbreak of Severe Acute Respiratory Syndrome (SARS) was at the start of the 21st century. It was caused by the SARS Corona virus (SARS-CoV-1) and started in China. It affected fewer than 10,000 individuals, mainly in China and Hong Kong, but also in other countries, including 251 cases in Canada (Toronto). The severity of respiratory symptoms and mortality rate of about 10% caused a global public health concern. Through the vigilance of public health systems worldwide, the outbreak was contained by mid-2003 [14]. This certainly is a sad statement when considering the virtually uncontrolled evolution and spread of the SARS-CoV-2 pandemic being experienced during the second decade of the 21st century. How can it have happened? The novel coronavirus (SARS-CoV-2), albeit more contagious than the SARS-CoV-1, was allowed to spread uncontrolled because of inadequate (personal responsibility and political accountability) attention to the simplest cardinal public health measures to control infectious disease − testing, quarantine, social distancing, copious hygiene (hand-washing), wearing masks and contact tracing. Such a sad statement has resulted in otherwise avoidable human suffering [15].

8.1.3 Incidence and prevalence of COVID-19

Originating in the City of Wuhan, China in December 2019, the novel coronavirus spread rapidly throughout China (epidemic) and within two months, it had spread throughout the entire world becoming a pandemic labeled COVID-19. At the time of this writing (August 31, 2020) this pandemic had spread to 213 countries and territories and has escalated to a total of 25,620,939 reported cases and 854,222 deaths worldwide and in the United States, 6,210,979 cases or 24% of the worldwide total and 187,713 deaths or 22% of the world's total [16,17]. In the United States, COVID-19 has already become the 3rd leading cause of death in 2020, behind heart disease and cancer. There is little doubt that when you read this book, these case numbers and mortality rates will have grown substantially, hopefully less than currently predicted.

8.2 Pathogenesis and bioscience considerations for SARS-CoV-2

8.2.1 Mechanisms

Viruses are not living cells or organisms. They are obligate parasites or non-living organisms that lack metabolic machinery of their own to generate energy or to synthesize proteins. Rather, they require a living host (an "obligate") to exploit or infect (enter) so they can replicate to complete their life cycle (see Fig. 8−1 and Life Cycle below). The invading virus uses either its genomic DNA or RNA to replicate in the host cell. Coronaviruses (CoV) are a family of RNA viruses that typically cause mild respiratory disease in humans. They include MERS-CoV and SARS-CoV-1, thought to be driven by the spillover of bat-adapted CoVs into an intermediate host (see below). The novel coronavirus (SARS-CoV-2) is a single positive-strand RNA virus which is the largest genome known. Thus, these viruses are poorly adapted to the human host and if transmitted to humans (e.g., SARS-CoV-2), they are generally associated with more severe clinical presentations. Also, if infection occurs, it can be highly transmissible from person to person as SARS-CoV-2 has demonstrated [18].

8.2.2 Theories

Several studies suggest that antibodies against non-SARS-CoVs are highly prevalent in the general population including children, suggesting that most individuals have been infected by CoVs and have potentially developed a certain degree of (protective) immune response [19]. The severity and the clinical picture could even be related to the activation of an exaggerated immune mechanism ("cytokine storm"), causing uncontrolled inflammation (i.e., the immune system as "our worst enemy"). The hypothesis that SARS-CoV-1 (or other, antigenically similar CoV-1) have silently infected a significant proportion of the population, inducing herd immunity (see "Treatment and management strategies" below) needs to be confirmed. Indeed, immunity against the infection, or also patterns of semi-immunity (capacity of the immune system to avoid severe infection) may be due to cellular rather than humoral immune responses.

Within 19 days after symptom onset, a total of 100% of 285 patients with COVID-19 tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM (transition of the test results for IgG or IgM against SARS-CoV-2 from negative to positive results in sequential samples) occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within six days after seroconversion [20]. Serological testing may be helpful for the diagnosis of suspected patients with negative RT−PCR results and for the identification of asymptomatic infections. Animal models suggest that the efficiency of T lymphocyte-mediated immune responses (see Chapter 6, page 4) is pivotal for controlling SARS-CoV infections [21].

There are currently no data on the specific role of either humoral or cellular immunity or innate immunity in patients recovering from COVID-19. T lymphocytes responsible for clinically relevant antiviral immune responses have a significant chance to be locally present in, or close to, respiratory epithelia [22]. It is very possible that the exclusive detection of humoral immunity against SARS-CoV-2 leads to an underestimation of the anti-SARS-CoV-2 immune responses. It becomes plausible that, after infection by SARS-CoV-2, a sort of race

decides the course of the events. Either a cellular innate immune response rapidly clears SARS-CoV-2 without any (or mild) clinical signs of infection, or the virus causes a state of immunosuppression that debilitates and sometimes overwhelms the host's defense [23].

San Francisco-based Vir Biotechnology has identified several human neutralizing monoclonal antibody (mAb) candidates against SARS-CoV-2. The lead antibody's ability to neutralize the SARS-CoV-2 live virus has been confirmed in two different laboratories. It binds to an epitope, the specific site on the viral antigen molecule that is also seen on the SARS-CoV-1 virus that causes SARS. This means the antigen is highly conserved and less likely to disappear should the viruses mutate or develop resistance to the antibody [24].

Researchers have analyzed genomic data related to the overall molecular structure of the new coronavirus. Their testing (AI machine learning karyotyping analysis) has traced this novel coronavirus to a strain of Malaysian anteater (pangolin) containing genomic regions that are very closely related to the human virus. Their analysis showed that the genome resembles that of a bat coronavirus discovered after the COVID-19 pandemic began. However, in "SARS-CoV-2 testing," the binding region of the spike protein resembles the novel virus found in pangolins (anteaters). This provides additional evidence that the coronavirus that causes COVID-19 almost certainly originated in nature, most likely in bats with an intermediate animal (anteater or monkey?) host and ultimately transmitted to humans ("zoonotic spillover") [25].

Most important among these findings is the receptor binding domain (spike protein) that dictates how the virus is able to attach and infect human cells (see Life cycle below). This comparative analysis of genomic data dispelled the postulate that the virus was laboratory constructed or was a "manipulated" virus. Rather, it promotes a lesson learned to reduce human exposure to wildlife and to ban the trade and consumption (e.g., "wet markets" in China) of wildlife. This genetic information concludes that "coronaviruses clearly have the capacity to jump species boundaries and adapt to new hosts (virus recently reported in Malaysian tigers in Bronx Zoo [26]), making it straightforward to predict that more will emerge in the future." However, as not all of the early COVID-19 cases were wet market associated, it is possible that the emerging story is more complicated than first suspected.

The genomic data of the new coronavirus responsible for COVID-19 show that its spike protein contains some unique adaptations. One of these adaptations provides special ability of this coronavirus to bind to a specific protein on human cells called angiotensin converting enzyme (ACE-2). Human ACE-2 is expressed in epithelial cells of the lung and serve as an entry receptor site for SARS-CoV-2 spike glycoprotein [27]. ACE-2 genetic polymorphism (occurrence of different forms in the life cycle of an individual organism.) represented by diverse genetic variants in the human genome, has been shown to affect virus-binding activity [28] suggesting a possible genetic predisposition to COVID-19 infection. Thus, machine learning analysis of genetic variants from asymptomatic, mild or severe COVID-19 patients can be performed to classify and predict people based on their vulnerability or resistance to potential COVID-19 infection. Furthermore, the machine learning model can also return those prioritized genetic variants, such as ACE-2 polymorphism.

The entire genome of the 2019-novel coronavirus is more than 80% similar to the previous human SARS-like bat CoV. Thus, previously used animal models for SARS-CoV can be

utilized to study the infectious pathogenicity of SARS-CoV-2. CRISPR-mediated (see CRISPR, Chapter 7, page 303 and below), genetically modified hamsters or other small animals can be utilized for the study of the pathogenicity of novel coronaviruses. In such studies, AI predictions can be used to investigate the inhibitory role of the drug against SARS-CoV-2 [29].

8.2.3 Life cycle of SARS-CoV-2

The pathogenesis and life cycle of SARS-CoV-2 includes a complex of RNA genomic transfers and regenerations to produce the proliferation of the virus. The extracellular and intracellular (host cytoplasm) process involved is illustrated in Fig. 8—1 and traced through the following steps:

1. When the spike protein of SARS-CoV-2 binds to the ACE-2 receptor of the host cell, the virus enters the cell;
2. Then the fatty envelope of the virus is peeled off, which releases the viral genomic RNA into the cytoplasm;
3. The ORF1a and ORF1b (genes) RNAs are produced by genomic RNA, and then translated into pp1a and pp1ab proteins, respectively;
4. Protein pp1a and ppa1b are cleaved by protease (proteolysis) to make a total of 16 nonstructural proteins;
5. Some of the nonstructural proteins form a replication/transcription complex (RNA-dependent RNA polymerase, RdRp), which use the (+) strand genomic RNA as a template;
6. The (+) strand genomic RNA produced through the replication process becomes the genome of a new virus particle;
7. Subgenomic RNAs produced through the transcription are translated into structural proteins (S: spike protein, E: envelope protein, M: membrane protein, and N: nucleocapsid protein) which form a viral particle;
8. Spike, envelope and membrane proteins enter the endoplasmic reticulum, and the nucleocapsid protein is combined with the (+) strand genomic RNA to become a nucleoprotein complex;
9. This complex merges into the complete virus particle in the endoplasmic reticulum-Golgi apparatus compartment; and
10. The new viral particles are released (exocytosis) to extracellular region through the Golgi apparatus and the vesicle.

8.2.4 Review of AI regarding the pathogenesis of SARS-CoV-2

1. Forbes Magazine reported on a global artificial intelligence database company, BlueDot, using an AI-powered algorithm, machine learning, and natural-language processing to analyze information from a multitude of sources that can track over a hundred infectious diseases [30].
2. AI is playing an important role in evaluating the pathogenesis, diagnosis and treatment of the SARS-CoV-2 virus. There is an urgent need to develop a system with AI-based machine learning capacity to analyze and integrate imaging-based, patient-based,

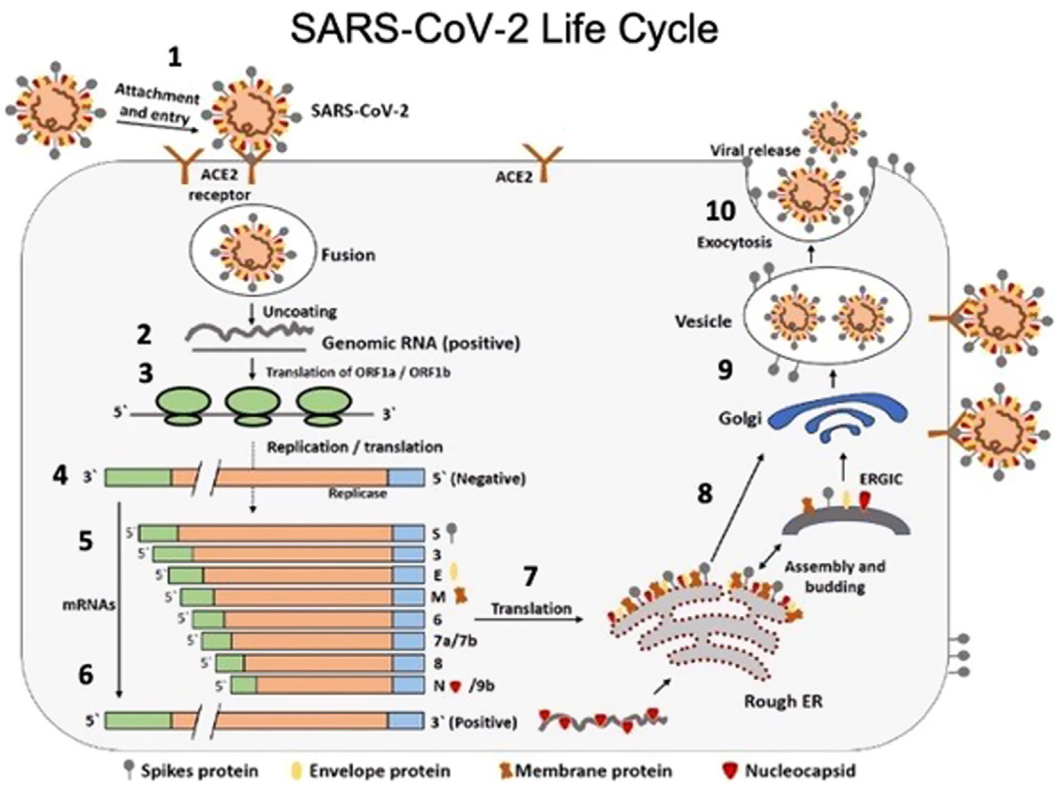

FIGURE 8–1 SARS-CoV-2 Life Cycle. The life cycle of the novel coronavirus (SARS-CoV-2) begins when its spike protein attaches to an ACE2 receptor on a cell membrane (1) and penetrates the cell wall where it replicates a genomic RNA (2−4), then produces 'subgenomic RNAs' (5−6), synthesizes various spike proteins through translation (7) and new genomic RNA becomes the genome of a new virus particle (8). This combines with the strand genomic RNA, merges in the endoplasmic reticulum-Golgi apparatus into a complete virus particle within a vesicle (9), and the new viral particles are released (exocytosis) to the extracellular region (10). *Source: Shereen MA. Khana S. Kazmi A. et al. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J. Adv. Research. 2020;24:91–98.*

clinician-based, and molecular measurements-based data, to fight the outbreak of COVID-19 and enable more efficient responses to unknown infections in the future [31].

3. Vaxign is a reverse vaccinology tool being used with Vaxign-ML machine learning tool to predict COVID-19 vaccine candidates. A study applied the state-of-the-art Vaxign reserve vaccinology (RV) and Vaxign-ML machine learning strategies to the entire SARS-CoV-2 proteomes including both structural and non-structural proteins for vaccine candidate prediction. The results indicate for the first time that many non-structural proteins could be used as potential vaccine candidates [32].
4. AI technologies are powerful tools against COVID-19 and widely used in combating this pandemic. A survey investigated the main scope and contributions of AI in combating COVID-19 from the aspects of disease detection and diagnosis, virology and

pathogenesis, drug and vaccine development, and epidemic and transmission prediction. AI mainly focuses on medical image inspection, genomics, drug development, and transmission prediction, and thus still has great potential in this field [33].

5. On March 16, 2020 the White House issued a call to action for global AI researchers to develop new algorithms and data mining techniques to assist in COVID-19 related research. Within a short period of time advanced machine learning techniques were developed and implemented to better understand the pattern of viral spread, further improve diagnostic speed and accuracy, develop novel effective therapeutic approaches, and potentially identify the most susceptible people based on personalized genetic and physiological characteristics. This is only the beginning of a permanent role AI will play in global health care [34].

8.3 Clinical considerations regarding SARS-CoV-2 infection

8.3.1 Clinical manifestations (signs and symptoms)

Reported illnesses with the novel coronavirus have ranged from mild symptoms to severe illness and death for confirmed COVID-19 cases. The symptoms may appear two to 14 days after exposure (based on the incubation period of SARS-CoV viruses). Symptoms include fever, cough and shortness of breath. Elderly and immune compromised patients are at greater risk for contracting the virus and for poor outcomes. However, significant numbers of young and healthy people are also being reported, though with generally better outcomes. Spread occurs through respiratory droplets produced when an infected person coughs or sneezes. These droplets persist in air for extended periods and can land in the mouths or noses of people who are nearby or possibly inhale the virus into their lungs.

Older age, obesity, and comorbidities have consistently been reported as risk factors for unfavorable prognosis or protracted disease ("long haulers"). Less clear so far has been how the number and types of comorbidities influence the outcome. An epidemiologic clarification was provided through a nationwide Chinese retrospective cohort study involving 1590 PCR-confirmed (see Antigen testing below) COVID-19 cases (mean age, 49 years; 43% female) diagnosed between December 11, 2019, and January 31, 2020. The most common symptoms were fever, dry cough, and fatigue (88%, 70%, and 43%, respectively). The mean incubation period was four days. According to the 2007 American Thoracic Society/Infectious Disease Society of America guideline for community-acquired pneumonia criteria, 16% of the cases were considered severe. Reported proportions with comorbidities included 17% hypertension, 8% diabetes, 4% cardiovascular disease, 2% cerebrovascular disease, 2% chronic obstructive pulmonary disease (COPD), 1% chronic kidney disease, and 1% malignancy. At least one comorbidity was significantly more common in severe than in non-severe cases (33% vs. 10%) [35]. Obesity puts those with coronavirus disease 2019 (COVID-19) at particularly higher risk of death, more so than related risk factors such as diabetes or hypertension, according to a study of patient records by researchers from Kaiser Permanente [36].

Coronavirus disease leads to fast activation of innate immune cells, especially in patients developing severe disease. Innate immune activation, levels of many pro-inflammatory

effector cytokines (e.g., TNF, IL-1β, IL-6, IL-8, G-CSF and GM-CSF), as well as higher levels of chemokines (e.g., MCP1, IP10 and MIP1α) are also found in those who are critically ill. In addition, the levels of some T cell-derived cytokines (e.g., IL-17) are increased [37]. A cytokine storm can develop that triggers a hyperinflammatory state. This inflammatory clinical response leaves virtually all organ systems vulnerable to adverse effects from the novel coronavirus. Of increasing concern are the cardiovascular effects resulting from perivasculitis (inflammation of the adventitia and endothelial lining of blood vessel walls – see Chapter 7, page 297) [38]. Anti-inflammatories (steroids) and cytokine inhibitor drugs (e.g., checkpoint inhibitors, IgG, Interleukin 6 blockers) are being studied and beginning to show some benefits in advanced cases and late stage disease [39].

AI is playing an important role in evaluating the pathogenesis, diagnosis and treatment of the SARS-CoV-2 virus. There is an urgent need to develop a system with AI-based machine learning capacity to analyze and integrate imaging-based, patient-based, clinician-based, and molecular measurements-based data, to fight the outbreak of COVID-19 and enable more efficient responses to unknown infections in the future [31].

8.3.2 Diagnostic testing

The clarion call during the early stages of the COVID-19 pandemic was "Testing, Testing, Testing." Tracking ("contact tracing") an invisible virus is the only way to control it, and the most effective strategy to accomplish that goal starts with building a comprehensive system to test anyone who may be infected. Upon accomplishing that, then those positive cases can be isolated and "contact traced" (identifying persons who may have come into contact with the infected person) and testing them as well and isolate all positive cases. This critical "diagnostic" process is conducted through two types of tests, one testing for the antigen (people who are currently infected) and second, testing for antibodies to the antigen (people previously infected who have developed antibodies to the virus).

Continuing efforts are being made to develop novel diagnostic approaches to COVID-19 using machine learning algorithms. Machine learning based screening of SARS-CoV-2 assay designs using a CRISPR-based virus detection system are demonstrating high sensitivity and speed. Neural network classifiers have been developed for a large-scale screening of COVID-19 patients based on their distinct respiratory pattern. Also, a deep-learning based analysis system of thoracic CT images was constructed for automated detection and monitoring of COVID-19 patients over time. Rapid development of automated diagnostic systems based on AI and machine learning can not only contribute to increased diagnostic accuracy and speed, but will also protect healthcare workers by decreasing their contacts with COVID-19 patients.

8.3.2.1 Antigen testing

An antigen test reveals if a person is actively infected with the SARS-CoV-2 virus. The test detects certain proteins that are part of the virus. Using a nasal or throat swab to get a fluid sample, antigen tests can produce results in minutes. Because these tests are faster and less

expensive than molecular tests, some experts consider antigen tests more practical to use for large numbers of people. Once the infection has gone, the antigen disappears. A positive antigen test result is considered very accurate, but there's an increased chance of false negative results, meaning it's possible to be infected with the virus but have negative antigen test results. So, antigen tests aren't as sensitive as molecular tests. This type of test already exist for strep throat, influenza, tuberculosis, HIV, and other infectious diseases [40].

8.3.2.2 Molecular genetic test (PCR test)

This test detects genetic material of the virus using a lab technique called polymerase chain reaction (PCR). Also called a PCR test, a health care worker collects fluid from a nasal or throat swab or from saliva. Results may be available in minutes if analyzed onsite or one to two days if sent to an outside lab. Molecular tests are considered very accurate when properly performed by a health care professional, but the rapid test appears to miss some cases. The FDA also approved certain COVID-19 at-home test kits, available only with doctor approval. It can be done with a nasal swab kit or a saliva kit. The sample is mailed to a lab for testing. The FDA warns consumers against buying unapproved home tests, because they may be inaccurate and unsafe [41].

8.3.2.3 Antibody testing

Antibody tests check a person's blood by looking for antibodies, which may (or may not) tell if the person had a past infection with the coronavirus. Antibodies are proteins that help fight off infections and thus, can provide immunity and protection against getting the infection again (this is uncertain). Neutralizing antibodies are specific to an antigen (the virus) and thus, provide protection only against the specific disease associated with the antigen (in the case of coronavirus as the antigen, the disease being COVID-19). If the person is exposed to the antigen (coronavirus) again, the antibodies produce "memory" (anamnestic protection) towards the disease [42]. However, there are increasing reports of reinfection with the novel coronavirus suggesting that some coronavirus antibodies may not be neutralizing antibodies [43].

Except in instances in which viral testing is delayed, antibody tests should not be used to diagnose a current COVID-19 infection. An antibody test may not show if you have a current COVID-19 infection because it can take one to three weeks after infection for your body to make antibodies. To see if you are currently infected, you need a viral test. Viral (antigen) tests identify the virus in samples from your respiratory system, such as a swab from the inside of your nose. It is possible to isolate the coronavirus from respiratory secretions, blood, urine, and fecal samples for diagnostic testing. Clinically, infections can be diagnosed with respiratory viral panels that are widely commercially available [44].

8.4 Treatment and management strategies

Care for coronavirus patients is supportive in nature and may include supplemental oxygen, fluid administration, and, for critically ill patients, being managed in intensive care units and receiving rescue therapies such as extracorporeal membrane oxygenation (pulmonary ventilation). Stringent infection control is critical to preventing transmission to healthcare workers

and other patients. Droplet precautions (e.g., personal protective equipment [PPE] including surgical or procedure mask, gown, and gloves) are indicated during the treatment of all coronavirus patients, and such protocols for droplet-spread respiratory viruses are part of hospital infection control practices. Additional respiratory precautions may also be appropriate during aerosol-generating procedures [45].

At the time of the writing of this chapter on COVID-19, treatment and management strategies continue to grow, some proving effective and some ineffective. In that this is being written at the height of the pandemic (late 2020), it must be considered a prospective view of appropriate treatment and management as recommended by the medical experts guiding us through this difficult period. It will be of interest to the readers in the months and years ahead, to evaluate retrospectively, which of these treatment and management approaches proved most value. Hopefully, it will be a prescient lesson to future generations in their preparedness and response to epidemics and pandemics they may face. Future readers of this book will be able to retrospectively assess the strengths and weaknesses of each.

8.4.1 General measures

8.4.1.1 Basic preventive steps

1) Shelter-in-place or "self-isolation" (remain in your home with only absolutely necessary outdoor activities);
2) Social distancing (separation of >6 feet between people);
3) Wash your hands copiously and frequently;
4) Face masks (first CDC and surgeon general suggest for use only if infected, now strongly recommended for fulltime use);
5) If symptoms occur (fever, cough, chills, aches and pains), get tested and if positive, self-quarantine for minimum 14 days and retest $\times 2$ before assuming normal activities;
6) If symptoms advance over two to three days, seek medical attention.

8.4.1.2 Mitigation

This term describes the procedures and policies to reduce risks of infectious spread. Results of mitigation are measured by "flattening the curve," i.e., the inverted bell-shaped curve that is produced in a bar graph measuring increases (and eventual decreases in the number of positive cases on a daily basis). This curve also can measure a percentage of positive cases resulting from testing. This is a significant measure as to effective control of viral spread.

8.4.1.3 Contact tracing

Epidemiologists ("disease detectives") attempt to identify potential "spreaders" by identifying the index patient, sometimes called "patient zero." Depending on what they already know about that patient's condition — how the disease is spread, its natural history, what symptoms it causes — they interview the patient to learn about their movements and identify all

close contacts (persons, places and things). Based on the answers, public health workers contact each associated person (having had contact with the index patient to explain their risk, offer screening for the infection and conduct regular monitoring for symptoms of the infection. This important public health measure is not progressing well (late 2020) due to limited "tracer personnel" and public resistance to sharing information.

8.4.1.4 Modeling

1) Study the mechanisms by which disease is spreading;
2) Monitor (graphically) through testing positive case volumes, death rates and other vital statistics [45];
3) Predict the future course of an outbreak;
4) Mitigation; and
5) Evaluate strategies to control an epidemic. Modeling data produces an inverted bell shape curve with the x-axis representing time and the y-axis representing number of cases.

8.4.1.5 Herd immunity and R Naught (RO or R_O)

The concept of herd immunity is an epidemiological formula in which a sufficient amount of people are immunized or vaccinated against a pathogen, thus reducing the rate of infection throughout the population. The vaccination levels must produce a threshold called the "R-Naught" or R_O (The SIR ['susceptible-infectious-recovered']) formulation, a factor that determines the transmissibility of the pathogen. It denotes the average number of secondary cases of an infectious disease that one case would generate in a completely susceptible population. That is, when one infected person infects greater than one other person, a potential exponential increase in infections results leading to an epidemic or pandemic. If, however, transmission on average remains below an R_O of one person, this will result in a decreasing spread in infection and eventually into a majority of the population (an estimated 60−70% needed) to produce "herd immunity" [46].

In the absence of a vaccine, developing herd immunity to an infectious agent requires large amounts of people actually being infected, developing antibodies to the infectious agent and thus, becoming immunized against future infection. Scientists are not always certain if this immunity is permanent or for how long it might last. But even assuming that immunity is long-lasting, a very large number of people must be infected to reach the 60−70% herd immunity threshold required. During this process, mortality of certain infections like SARS-CoV-2 could reach unacceptable levels as occurred in Sweden [47].

Nor does a pathogen magically disappear when the herd immunity threshold is reached. Rather, it only means that transmission begins to slow down and that a new epidemic is unlikely to start up again. An uncontrolled pandemic could continue for months after herd immunity is reached, potentially infecting many more millions in the process. These additional infections are what epidemiologists refer to as "overshoot" [47].

8.4.2 Therapeutics

8.4.2.1 Monoclonal antibodies

Monoclonal antibodies (any drug with the name suffix, "...mab") are laboratory engineered antibodies by Regeneron, Eli Lily, et al. used to mimic the immune system's own antibodies for a specific antigen. These antibodies are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody). Rather than wait for vaccines to coax the body to make its own antibodies, scientists are studying versions of these molecules to directly disable the SARS-CoV-2 coronavirus [48].

Monoclonal antibodies are nowadays often generated by isolating or transforming antibody-producing cells taken directly from immunized animals or patients, and transplanting the antibody-encoding genes of these cells into suitable producer cell lines, rather than using hybridoma technology [49].

8.4.2.2 Convalescent plasma (serum)

Plasma is collected from patients who recovered from COVID-19. Each donates a pint of blood. The red and white blood cells are separated and put back into the donor's bloodstream while the blood plasma, rich with virus-fighting antibodies, is kept aside [50]. Four hundred and three monoclonal antibodies were isolated from three convalescent COVID-19 patients. They showed that the patients had strong immune responses against the viral spike protein, a complex that binds to receptors on the host cell. A subset of antibodies was able to neutralize the virus [51]. Early results, (late 2020) however are proving questionable.

8.4.2.3 Hydroxychloroquine (Plaquenil®) combined with azithromycin (Zithromax®)

A small sample survey showed that hydroxychloroquine treatment (a biologic used for malaria and lupus) is associated with viral load reduction in COVID-19 patients and its effect is reinforced by azithromycin (an antibiotic). A study reported in the New England Journal of Medicine conclude that results do not support the use of hydroxychloroquine at present, outside randomized clinical trials testing its efficacy [52]. Further work is warranted to determine if these compounds could be useful as chemoprophylaxis to prevent the transmission of the virus without significant adverse effects [53]. Continuing testing however is indicating increased risks of adverse cardiac effects with this form of therapy.

8.4.2.4 Remdesivir

This drug is thought to interfere with the mechanism that coronavirus uses to make copies of itself (see Fig. 8.1 and discussion on Life Cycle above). Scientists are still working out exactly how that occurs. A preliminary report published in The New England Journal of Medicine showed that the drug shortened recovery time for people with COVID-19 from an average of 15 days to about 11 days [54]. Issues of storage, supply and cost of this drug are presenting serious limitations on its long term value.

8.4.2.5 Dexamethasone (and corticosteroids)

As discussed above and in detail in Chapter 6, chronic inflammatory organ injury (e.g., heart, lungs, kidneys) may occur in severe Covid-19, with a subgroup of patients having markedly elevated levels of inflammatory markers. Several therapeutic interventions have been proposed to mitigate inflammatory organ injury in viral pneumonia including glucocorticoids (i.e., dexamethasone). Glucocorticoids have been widely used in syndromes closely related to Covid-19, including SARS, Middle East respiratory syndrome (MERS), severe influenza, and community-acquired pneumonia. However, the evidence to support or discourage the use of glucocorticoids under these conditions has been weak [55]. In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [56]. Other steroids and biologic agents are also beginning to show some promising results [57].

8.4.2.6 RNA screening

SARS-CoV-2 is an RNA virus which means its genetic material is encoded in RNA. Once the virus is inside our cells, it releases its RNA and making long viral proteins to compromise the immune system (see Life Cycle above). The virus assembles new copies of itself and spreads to more parts of the body. One of the weapons in our cells' is an RNA surveillance mechanism called nonsense-mediated mRNA decay (NMD) that protects us from many genetic mutations that could cause disease. The genome of COVID-19 is a positive-sense, single-stranded RNA which can evade NMD and prevent it from degrading RNA by producing proteins that interacts with certain proteins that modify the chemical structure of RNA. With the progression of new viral strains, this research on the fundamentals of RNA allows for the development of therapeutics and vaccines that directly target processes critical to a virus's life cycle (see Fig. 8.1, page 451) [58].

8.4.3 Vaccine (immunization)

By definition, a vaccine is a biological preparation that provides active, adaptive immunity to a particular infectious disease (e.g., SARS-CoV-2) by stimulating neutralizing antibodies to the source of the infection. It typically contains an agent that resembles the disease-causing microorganism made from weakened or killed forms of the microbe (an attenuated virus), its toxins, or one of its surface proteins. The spike protein is the target for most of the COVID-19 vaccine human clinical trials and so research centers on how the immune system, particularly B and T cells, responds to the spike protein. B cells are responsible for producing the antibodies that recognize SARS-CoV-2, while T cells play an important role in supporting the development of the B cell response (see Chapter 7).

Vaccination is the act of getting a vaccine, usually as an injection to immunize a person (immunization) to protected against a disease. Testing for an effective vaccine begins with giving the vaccine to animals such as mice or monkeys to see if it produces an immune response. Then Phase One vaccinates a small number of people to test safety and dosage as

well as to confirm that it stimulates the immune system. Phase Two includes hundreds of people split into groups (viral injected and placebo), such as children and the elderly, to see if the vaccine acts differently in them as well as safety and ability to stimulate the immune system. Phase Three gives the vaccine to thousands of people (again, two groups) to see how many become infected, compared with volunteers who received a placebo. These trials can determine any rare side effects that might be missed in earlier studies. Finally, if the vaccine protects against the coronavirus in at least 50% of vaccinated people it is considered effective and regulators decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorization before getting formal approval [59].

At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Around 25 groups say they are working on viral-vector vaccines. A virus such as measles or recombinant adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. Pfizer has recently reported 90% success (currently unconfirmed) with a genetic RNA vaccine. Such vaccine types require deep freeze storage (− 94°F) and second (after 28 days) dose [60]. Finally, many researchers are experimenting with injecting coronavirus proteins directly into the body to mimic the coronavirus's outer coat [61].

8.4.4 CRISPR-Cas13 and RNA screening

A new Cas13 RNA screen has been developed to establish guide RNAs for the COVID-19 coronavirus and human RNA segments which could be used in vaccines, therapeutics and diagnostics. A novel CRISPR-based editing tool enables researchers to target mRNA and knockout genes without altering the genome has been developed. Using the CRISPR-Cas13 enzyme, researchers have created a genetic screen for RNA, currently designed for use on humans, which they say could also be used on RNA containing viruses and bacteria.

The developers have used their parallel-screening technique to create optimal guide RNAs for the SARS-CoV-2 coronavirus which could be used for future detection and therapeutic applications. The platform is optimized to run massively-parallel genetic screens at the RNA level in human cells because it is based on the CRISPR-Cas13 enzyme, which targets RNA instead of DNA. The data is collected by targeting thousands of different sites in human RNA transcripts to create a machine learning-based predictive model to expedite identification of the most effective Cas13 guide RNAs [62].

8.4.5 Immunoinformatics

AI and immunoinformatics (computational immunology) play a central role in vaccines by suggesting components understanding viral protein structures, and helping medical researchers scour tens of thousands of relevant research papers at an unprecedented pace [63]. AI supported preclinical studies in mice of a candidate vaccine based on this spike protein are already underway at NIH's Vaccine Research Center (VRC). But there will be many more steps after that to test safety and efficacy, and then to scale up to produce millions of doses. National Institute of Allergy and Infectious

Diseases (NIAID) is now working with the numerous biotechnology company (AstraZeneca, Pfizer, J&J, Moderna, et al.) to use the latest findings to develop a vaccine candidate using messenger RNA (mRNA), molecules that serve as templates for making proteins (see Pfizer news release above, page 459). The goal is to direct the body to produce a spike protein in such a way to elicit an immune response and the production of antibodies. Other forms of vaccine candidates are also in preclinical development [64].

AI and immunoinformatics are being used to better understand the structure of proteins involved in SARS-Cov-2 infection in search for potential treatments and vaccines. Proteins have a three-dimensional structure, which is determined by their genetically encoded amino acid sequence (Next-gen sequencing of genetic code), and this structure influences the role and function of the protein. An AI Google DeepMind system called AlphaFold [65] uses amino acid sequencing and protein structure to make predictions to construct a "potential of mean force" which can be used to characterize the protein's shape. This system has been applied to predict the structures of six proteins related to SARS-CoV-2 [66].

8.4.6 Review of AI for clinical considerations for coronavirus infections

1. Continuing efforts are being made to develop novel diagnostic approaches to COVID-19 using machine learning algorithms. Machine learning based screening of SARS-CoV-2 assay designs using a CRISPR-based virus detection system (see Cas13 above) are demonstrating high sensitivity and speed. Neural network classifiers have been developed for a large-scale screening of COVID-19 patients based on their distinct respiratory pattern. Also, a deep-learning based analysis system of thoracic CT images was constructed for automated detection and monitoring of COVID-19 patients over time. Rapid development of automated diagnostic systems based on AI and machine learning can not only contribute to increased diagnostic accuracy and speed, but will also protect healthcare workers by decreasing their contacts with COVID-19 patients [67].
2. Five companies were highlighted for developing deep learning models to predict old and new drugs that might successfully treat COVID-19. Scudellari M. Five Companies Using AI to Fight Coronavirus. IEEE Spectrum. March 19, 2020 [68].
3. Advanced deep learning-based CNN algorithms plays a major role in extracting highly essential features, mostly in terms of medical images. This technique, with using CT and X-Ray image scans, has been adopted in most of the recently published articles on the coronavirus with remarkable results. Furthermore, according to this paper, this can be noted and said that deep learning technology has potential clinical applications [69].
4. A new framework has been proposed to detect COVID-19 using built-in smartphone sensors (IoTs). The proposal provides a low-cost solution that ordinary people can use on their smartphones for the virus detection purposes. The designed AI enabled framework reads the smartphone sensors signal measurements to predict the grade of severity of the pneumonia as well as predicting the result of the disease [70].

5. AI and deep learning algorithms are being developed to enhance the detection and diagnosis of COVID-19. The need to provide access to accurate and low-cost tests for the diagnosis of COVID-19 is critical. Such AI algorithms can be used as an initial screening tool for suspected cases so that patients at higher risk could have confirmatory laboratory-based tests and be isolated if necessary. These algorithms could help health care providers triage patients with COVID-19 into potentially three groups: the 80% who have mild disease; the 15% who have moderate disease; and the 5% who have severe disease, including those at high risk of mortality. Finally, AI can facilitate the discovery of novel drugs with which to treat COVID-19 [71].

8.5 Epidemiology and public health considerations in COVID-19

8.5.1 Current epidemiologic considerations

The COVID-19 impact already indicates more disastrous effects than that of 2003 severe acute respiratory syndrome (SARS-CoV). Many countries (e.g., China, Singapore, Hong Kong, South Korea, Italy, Spain and the USA) have relied on an extrapolation of classic infection-control and public-health metrics to contain the COVID-19 pandemic, similar to those used for previous SARS pandemics. They range from extreme quarantine measures, "shelter-in-place," "social distancing," to painstaking detailed contact tracing with hundreds of contact tracers. However, these measures may not be as effective in 2020 for tackling the scale of COVID-19. Three vertically integrated digital and AI technologies are being introduced for monitoring, surveillance, detection, prevention of COVID-19, and to mitigate its spread and its direct and indirect impact to worldwide healthcare systems [71].

First, the Internet of Things (IoT) is providing a platform that allows public-health agencies access to data for monitoring the COVID-19 pandemic. For example, the 'Worldometer' [72] provides a real-time update on the actual number of people known to have COVID-19 worldwide, including daily new cases of the disease, disease distribution by countries and severity of disease (recovered, critical condition or death). Johns Hopkins University's Center for Systems Science and Engineering has also developed a real-time tracking map for following cases of COVID-19 across the world, using the data collected from US Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the European Center for Disease Prevention and Control, the Chinese Center for Disease Control and Prevention (China CDC) and the Chinese website DXY [73].

Second, big data is providing opportunities for performing modeling studies of viral activity and for guiding individual country healthcare policymakers to enhance preparation for the outbreak. Using three global databases, WHO International Health Regulations, the State Parties Self-Assessment Annual Reporting Tool, Joint External Evaluation reports and the Infectious Disease Vulnerability Index, health authorities are performing modeling studies of 'nowcasting' and forecasting COVID-19 disease activity throughout the world for public-health planning and control worldwide [74].

Third, digital technology is enhancing public-health education and communication. The government of Singapore has partnered with WhatsApp (owned by Facebook) to allow the public to receive accurate information about COVID-19 and government initiative. Multiple social-media platforms (e.g., Facebook and Twitter) are currently being used by healthcare agencies to provide 'real-time' updates and clarify uncertainties with the public. Also, some facial-recognition companies (e.g., SenseTime and Sunell) have adopted the thermal imaging−enabled facial recognition to identify people with an elevated temperature [31].

The initial reaction in many countries to COVID-19 is for healthcare facilities to reduce or even cease many clinical services, including closure of clinics and postponement of medical appointments or elective surgeries. However, such strategies cannot be sustained indefinitely if the COVID-19 pandemic extends beyond six months. Healthcare systems should plan to use digital technology 'virtual clinics' using telehealth consultations with imaging data uploaded from peripheral sites and interpreted remotely. This would ensure that patients continue to receive standard clinical care while reducing physical crowding of patients into hospitals. Chatbots staffed by health professionals can also provide early diagnoses as well as patient education. And blockchain technologies can coordinate hospital, clinics and pharmacy patient information [31].

Undoubtedly, by the time you read this book, the AI literature and more so, AI programs and research in the epidemiology, public health considerations, clinical aspects and immunological considerations regarding COVID-19 will have proliferated into a major body of new science and "disruptive technologies" [75]. Indeed, the re-emergence of yet another more virulent SARS-CoV virus and global pandemic emphasize the ongoing and permanent challenge that infectious diseases pose and the need for global cooperation, AI and preparedness, even during "interim" periods.

Besides classic public-health measures for tackling the COVID-19 pandemic, in 2020, a wide range of digital technology are being implemented that can augment and enhance these public-health strategies. This COVID-19 health care crisis of 2020 provides a distinct opportunity to enhance the applications of AI technologies for immunology in the public health domain.

8.5.2 Review of AI for epidemiology and public health considerations

There are, however, inherent problems with AI solutions amid a pandemic. Many articles inflate AI's "effectiveness and scale," ignores the levels of human involvement, and sometimes demonstrates careless assessment of related risks. Taking it even further, the Brookings Institute suggests that "the COVID-19 AI-hype has been diverse enough to cover the greatest hits of exaggerated claims around AI" [76]. They list eight considerations for how to remain critically-minded and realistic amid all the AI-coronavirus hype:

1. Look to the subject-matter experts;
2. AI needs lots of data;
3. Don't trust AI's accuracy;
4. Real-world deployment degrades AI performance;
5. Most predictions must enable an intervention to really matter;

6. AI is far better at minute details than big, rare events;
7. There will be unintended consequences;
8. Don't forget: AI will be biased.

While taking a cautious approach to AI's role in an evolving health care crisis, we must also consider its enormous contribution to the scientific, clinical and public health platform it provides.

When the Covid-19 pandemic enters dangerous new phases, the critical question becomes whether and when to take aggressive public health interventions to slow down the spread of COVID-19. A study was undertaken to develop AI inspired methods for real-time forecasting and evaluating intervention strategies to curb worldwide spread. A modified autoencoder for modeling the transmission dynamics of the epidemics is being developed and applied to the surveillance data of cumulative and new Covid-19 cases and deaths from WHO, as of March 16, 2020. Total peak number of cumulative cases and new cases in the world with later intervention could reach 255,392,154 by January 2021. However, the total peak number of cumulative cases in the world with one-week earlier intervention were reduced to 1,530,276. We observed that delaying intervention for one month caused the maximum number of cumulative cases to increase 166.89 times, and the number of deaths increase from 53,560 to 8,938,725. Disastrous consequences if immediate action to intervene is not taken [77].

MIT published a paper describing the needed changes in three areas if we want AI to be useful in future pandemics. First, prediction through database companies using a range of natural-language processing (NLP) algorithms to monitor news outlets and official health-care reports in different languages around the world; second, machine-learning models with large datasets for examining medical images to catch early signs of disease that human doctors miss, from eye disease to heart conditions to cancer; third, identifying cures through big data analysis of drug trials and design algorithms to highlight biological and molecular structures matching drugs with candidates [78].

There have been multiple citations regarding AI and COVID-19 in this chapter. However, it would not be complete without a direct reference to deep learning and the diagnosis and treatment of the coronavirus. An article dated June 12, 2020 "offers a response to combat the virus through Artificial Intelligence (AI)." It identifies AI platforms for use by physicians and researchers to accelerate the process of diagnosis and treatment of the COVID-19 disease. Some include Deep Learning (DL) methods, Generative Adversarial Networks (GANs), Extreme Learning Machine (ELM), and Long/Short Term Memory (LSTM) and integrated bioinformatics approaches with different aspects of information from a continuum of structured and unstructured data sources. The main advantage of these AI-based platforms is to accelerate the process of diagnosis and treatment of the COVID-19 disease. The most recent related publications and medical reports were investigated to facilitate reaching a reliable Artificial Neural Network-based tool for challenges associated with COVID-19. There are some specific inputs for each platform, including various forms of the data, such as clinical data and medical imaging which can improve the performance of the introduced approaches toward the best responses in practical applications [79].

Conclusion

I began this chapter by reporting on the number of worldwide COVID-19 recorded cases and deaths to date. The number reminds me of a sad saying. "One death is a tragedy — 854,222 is a statistic." We can't let ourselves think that way. Maybe if we think of it as 854,222 personal tragedies (and growing), we'll realize what the world and each of us as caring individuals are truly enduring with this pandemic. How bad will it get? Unless a vaccine has been developed, approved and delivered to the world's population by the time you read this, we will continue to face human tragedies, not statistics, of epic proportions. It is estimated that there are 1.7 million viruses residing in environmental ecosystems throughout the world. Let us all hope and pray that the applications of science, AI technologies and mostly, our personal and societal efforts meet and defeat this public health challenge of infectious disease pandemics and help humanity create a better place for all.

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