Introduction

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The end of 2022 marked three years since the first reports appeared in the news of a potentially novel coronavirus in a seafood market in Wuhan, China. Commencing in December 2019, COVID-19 – caused by the severe acute respiratory disease coronavirus 2 (SARS-CoV-2) – spread rapidly across continents, with the first case of COVID-19 being reported in the United States as early as January 20, 2020. Two months later, with the official announcement being made by the World Health Organization, there was no denying the reality that we were in the midst of a raging pandemic.

At its inception, no one could have predicted the power of the virus. It swept through humanity, infecting more than 700 million people, killing more than 6.9 million people across 215 countries, cutting across caste, creed, and color.

This book is a tribute to the "warriors" who worked in the trenches day and night to combat the virus and wage the deadly war against the pandemic. It is meant to serve as a sobering reminder of the sacrifices made by so many. We dedicate this book to the millions of lives that were lost to COVID-19 and to frontline workers across the globe who sacrificed their lives in the line of duty.

This is our story of how humanity came together during an incredibly challenging time to unite forces and fight a common enemy. It is a story of reflections and lessons learned, a record of what we did right and what we could have done better, but, above all, this is a story that is written in gratitude to the unconquerable spirit of humankind and the relentless pursuit of scientific knowledge to serve humanity.

This book chronicles the power of innovation, the accelerated commercialization of diagnostics, the birth of new business models and creative financing ventures, the perseverance and commitment of entrepreneurs, and the agility and resourcefulness of government institutions as they adapted to meet the imminent needs of the pandemic and serve the community.

Coronaviruses are not new to humankind. Humanity has witnessed three deadly pandemics in the twenty-first century alone, all of which were associated with this group of viruses. In 2002, the world witnessed the first lethal coronavirus-induced disease, which was named severe acute respiratory syndrome coronavirus (SARS-CoV). A decade later, in 2012, a different coronavirus outbreak unraveled in the Middle East, earning the name Middle East respiratory syndrome coronavirus (MERS-CoV). Despite our seeming familiarity with this group of viruses, the global community was unprepared when a novel coronavirus reared its ugly head and swept through humankind with a ferocity last witnessed only during the Spanish influenza pandemic of 1917 caused by the H1N1 virus and often referred to as the greatest medical holocaust in history.

Despite previous appearances, this coronavirus was labeled as novel because a comparison of the viral genome revealed that it had only 79.5% homology with SARS-CoV and 40% homology with MERS-CoV. Thus, it was battle time again. We had no armamentarium to fight the virus or any specialized knowledge of what we were dealing with. Our understanding of the evolution of SARS CoV-2 and how it spread was particularly unclear during the early stages of the COVID-19 pandemic. Misconceptions and myths about its origin and its mode of transmission raged like wildfires across continents, fueling panic and chaos.

The pandemic had made its way into the life of the masses, and the scientific community was forced to meet the demands of questioning and angry communities demanding answers. Whatever side of the fence one was on with regard to the quality of scientific rigor on social media, it cannot be denied that the media served to disseminate knowledge and information at an unprecedented speed.

In the world that we live in today, where COVID-19, social distancing, lockdowns, contact tracing, super spreader events, antigen tests, and polymerase chain reaction (PCR) tests have all become common household parlance, let us not forget that, in December 2019, the world was a different place. Awareness of pandemics was at an all-time low, despite the occasional visionary messages of caution that were voiced by a select few but largely neglected.

The depth and breadth of scientific knowledge that we have amassed since that fatal day that SARS-CoV-2 interrupted humanity serves as a tribute to all the scientists, clinicians, and health-care workers who worked tirelessly at an unprecedented pace to advance coronavirus research. During its early spread in January, thousands of viral genomes were rapidly sequenced by research laboratories around the world and shared in open-access databases such as the EpiCoV database from the Global Initiative on Sharing All Influenza Data (GISAID) and the Our World in Data COVID-19 dataset. Within a month of the release of the SARS CoV-2 genome, the CDC had developed the first SARS-CoV-2 diagnostic test kit which got FDA EUA approval on February 4, 2020.

A glimmer of hope arose that widespread testing and early detection might serve to intervene in disease progression and thus counteract the increasing mortality that humanity was witnessing. Accordingly, many countries rushed to implement population-based testing to monitor spread and implement quarantining to reduce viral transmission. This created enormous pressure for high-quality, reliable tests to be developed and commercialized at record-breaking pace. The planet morphed into the largest global testing ground for humanity. Governments across the world rose to the occasion, as they have traditionally done, to fund research and innovation. From sequencing the SARS-CoV-2 genome and sharing it with the world to characterizing methods of viral entry and spread, as well as ongoing surveillance of an assault of viral variants and dealing with the confusion and utter despair of those who were asymptomatically spreading the virus, the scientific community worked tirelessly to push the boundaries of understanding the biology of the virus.

The chapters in this book are written by a wide range of authors with varying experiences and expertise, who have worked across the spectrum from research and development to commercialization of COVID-19 diagnostics. Given the multidisciplinary nature of this initiative, each chapter has been written by authors with relevant expertise and provides an in-depth narrative from their own unique perspectives. The chapters have been compiled to take the reader on a journey with us as we chronicle the early stages of the pandemic, the historical events, and the effectiveness of the decision-making processes during crucial

phases of the pandemic. We delve briefly into the immunology of the virus and its rapid evolution through mutagenesis and touch upon the controversial topic of immunity to the virus.

In the United States, SARS-CoV-2 spread rapidly, and with it grew the inability to keep pace with the increasing demands for COVID-19 diagnostic testing. In April 2020, as mortality continued to soar and the need for testing within the United States became imminent, the National Institutes of Health (NIH) received a $1.5 billion appropriation from Congress to expand testing capacity in the USA. Thus, it was that, while the world continued to operate in a chaotic frenzy, a new innovative program was born within five days after the legislation was signed into law.

The NIH launched the Rapid Acceleration of Diagnostics (RADx®) program. The RADx Tech initiative was created to support the development, validation, production, and commercialization of accurate, point-of-care, and home tests, as well as to improve existing clinical tests that could detect SARS-CoV-2. This brainchild initiative pushed diagnostics, a much-neglected sector, to the forefront through a focus on the compression of a diagnostic prototype-to-product launch from over five years to under a year. Many of the chapters in this book are written by authors who were part of the RADx initiative and worked in the trenches. These chapters go into intricate detail on each aspect of the journey, from development to deployment, and what it took to accelerate diagnostic capacity in a time of crisis.

Overall, the RADx Tech initiative was an unprecedented program that invested a huge amount of capital into COVID-19 diagnostics across the spectrum, from tests performed in reference laboratories to point-of-care diagnostics and over-the-counter home tests. The program used a rigorous "deep dive" diligence process and a "shark tank" model run by leading industry experts to select companies and projects with innovative technologies that had the potential to scale up and address the testing needs in different segments of society. Beyond the capital investments, RADx Tech proved to be a fertile ground for the evolution of a public–private partnership model such as the industry had not witnessed before. Combining the best of both worlds, it set out on its mission not just to finance innovation in companies and de-risk technology, but to provide companies with an ecosystem built to maximize success in commercialization. Its focus on external verification and validation through key institutions, data-driven go/no-go decisions, stringent timelines, and outcomes was responsible for the success of the program.

Another unique aspect of the initiative was the leverage of the Point-of-Care Technology Research Network (POCTRN), run by the National Institute of Biomedical Imaging and Engineering (NIBIB), which through three cycles of prior NIH funding had previously identified a critical gap in diagnostic device development around the clinical use case. Thus, as companies developed their technologies for COVID-19 tests, they were guided by experts in the areas of infectious disease and emergency medicine; ambulatory, pediatric, and adult clinicians; medical directors of certified laboratories; diagnostic developers; and marketing experts with real-world experience. At the time of writing this book, hundreds of millions of COVID-19 tests have been developed and marketed.

It was initially thought that, with SARS-CoV-2 being well adapted to humans, there was minimal need for concern about mutations among circulating viruses (because of the historically slow mutation rate of coronaviruses and their inherent self-editing mechanism). This changed during the later months of 2020, when the first reports appeared of emergent SARS-CoV-2 variants that were associated with increased transmissibility and disease severity.

Diagnostic tests, which were based on the original Wuhan sequence of SARS-CoV-2, were found to be affected by these mutations. The repeated emergence of new SARS-CoV-2 variants presented challenges to the development of high-performing diagnostics. The RADx Variant Task Force – an interdisciplinary group composed of representatives of federal agencies, diagnostic device manufacturers, private and public bioinformatics companies and organizations, large laboratory organizations, and academic institutions – was thus created as a program within the larger RADx initiative that focused on assessing RADx technologies against variants.

The clinical management chapter (Chapter 3) focuses on patient care during a time of absolute crisis and the significant shift in clinical practice from using evidence-based medicine to being forced to use experimental methods of treatment. It highlights the innovation in health-care delivery models as hospital leaders sought to incorporate telemedicine to widen patient reach while not compromising on quality.

A quote from George Santayana (*The Life of Reason*, 1905) comes to mind: "Those who do not remember the past are condemned to repeat it." So, let us not forget. Let us never cease to remember the sacrifice of doctors, health-care workers, and frontline responders across the globe. Humanity will always be grateful to them for their sacrifice during these unprecedented times. This book captures case studies of how strong and selfless leaders made it their mission to focus on the care of patients in a time when there were no rules on how to combat this enemy.

Can we prevent the next pandemic? As we continue to reflect on that question, we look back not just at the mistakes that were made during the pandemic but also at what we did right and the key contributions that were made in this period. A few of the noteworthy successes include but are not limited to controlling supply-chain bottlenecks, the rapid commercialization of diagnostics in a time of crisis, the unprecedented rollout of COVID-19 testing, vaccine development, accelerated regulatory approvals, and ensuring that affordable tests were made available as much as possible. A key differentiator of this book is the fact that, in each chapter, readers will find meticulously detailed roadmaps that are specific to the chapter. We hope that these will serve as useful tools for the next generation of health-care leaders to create, implement, and execute operational strategies in the face of chaos and uncertainty during successive disease outbreaks.

We are cognizant of the fact that, in this book, we have analyzed the pandemic through what could be considered a very US-centric lens. While part of this was choice, a large part of it was necessity. To be able to communicate with our readers with the experience and expertise that is required to tell this story, we had to write it from the battlefield we operated from, which was the United States. In no way do we mean to diminish the heroic efforts of other nations that fought this battle, and they should be applauded. Where possible, we have referenced global efforts and drawn attention to them in select chapters.

A pandemic affects various aspects of society. The closure of essential and nonessential businesses, restrictions on travel, requiring individuals to isolate to combat rising rates of mortality and morbidity all took their toll, and society faced existential threats as economies began to shut down. Varied national responses to the threat of the virus, as well as economic and racial differences across nations, led to societal disparities and vastly different pandemic impacts across the globe. This has not been ignored and is also a focus of this book.

There is no doubt in anyone's mind that the effect of the pandemic have been severe, and we are still witnessing and will continue to witness its long-term damage to society worldwide. The power of sharing scientific data, the strength of partnerships, the creativity

of collaborations, and the refusal to admit defeat in the presence of a common enemy should never be forgotten. These memories will serve us well for building a better and more resilient world.

Through this book, we hope to address the main components of the pandemic as it evolved and to provide strategies and guidelines for the management of outbreaks beyond COVID-19, thus serving as a legacy for many future generations.

Chapter 1

Early Detection, Response, and Surveillance of the COVID-19 Pandemic Crisis

Enrique M. Rabellino, Alexandra Smith, and Marta C. Cohen

Introduction

This chapter provides foundational knowledge of the occurrences, events, and disease manifestations during the early stages of the COVID-19 pandemic, including the responses and measures that were undertaken to contain the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. The importance of early intervention is discussed throughout this chapter to illustrate the impact that timely action – or, in many cases, inaction – had on the development of the pandemic. This chapter explores the data collection and analysis mechanisms utilized to monitor disease spread in different geographies. The necessity of information that is derived from early disease vigilance and subsequent surveillance programs is stressed. This chronological account is intended to create a roadmap for health and governmental authorities to follow for future undertakings, programs, and decision-making processes at the earliest phases of future pandemics.

Disease Outbreak

The spread of infectious diseases affects both individuals and entire communities. Early detection of a new outbreak is crucial so that containment measures can be implemented quickly enough to minimize the need for large-scale quarantine, especially when resources are limited. When primary care, public health, laboratories, and involved communities collaborate effectively, early identification and mitigation initiatives are achievable. This section outlines the initial detection of the COVID-19 outbreak and the responses of governments, public health officials, and communities. Figure 1.2 is designed to help visualize the significant occurrences during the earliest phases of the COVID-19 pandemic.

First Cases

On December 19, 2019, a case of pneumonia of unknown origin was detected in Wuhan, China, a city of 11 million people and the capital of Hubei province in central China. By December 29, 2019, four more cases had been reported to the Chinese Center for Disease Control and Prevention (CCDC).[1] All initially reported cases were related to the Wuhan South China Seafood Market (Huanan Seafood Wholesale Market). These cases had been identified through a surveillance mechanism for "pneumonia of unknown etiology," a concept designed to allow timely identification of novel infectious organisms introduced following the 2003 SARS-CoV outbreak.[2] Due to varying disease severity and clinical manifestations, these cases attracted the attention of local physicians. While little was known about the cause of these infections, there were indications of a possible new emerging virus that diverged from the classical influenza virus.

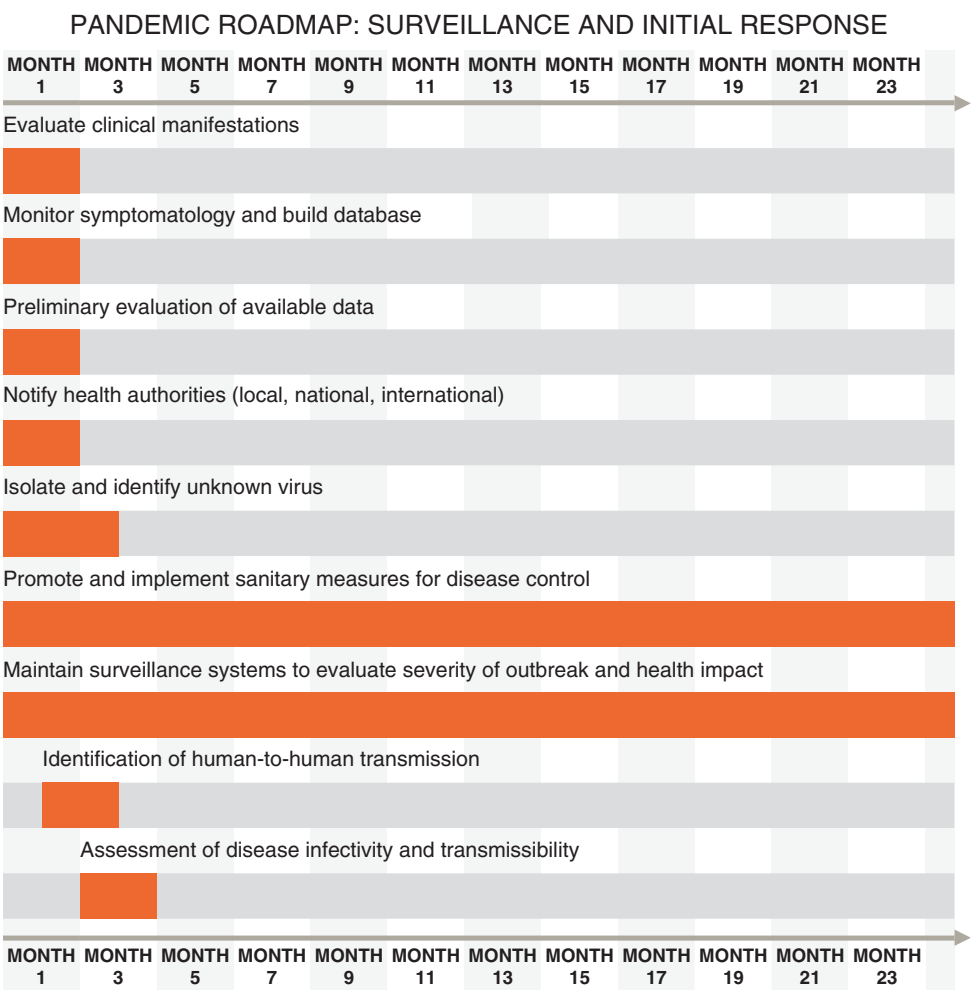

Figure 1.1 This roadmap depicts the vital activities, their chronology, and an estimated time frame in months. In the case of the SARS-CoV-2 pandemic, month 1 was December 2019, the month in which the virus was isolated, sequenced, identified, and published.

Roughly 10 days later, the medical administration of the Wuhan Municipal Health Commission (http://wjw.wuhan.gov.cn/) issued and distributed a document announcing the outbreak, reporting 27 new cases of pneumonia, mostly in stallholders at the Wuhan South China Seafood Market. Seven of these patients were in critical condition. Various hospitals in Wuhan held emergency symposia, where they defined a suspected case as a patient who met all four of the following criteria: fever, with or without recorded temperature; radiographic evidence of bilateral pneumonia; low or normal white blood cell count or low lymphocyte count; and no improvement in symptoms after three days of antimicrobial treatment, as per standard clinical guidelines. A patient who met the first three criteria and had an epidemiological link to the Wuhan South China Seafood Market could also be considered a suspected case.[3]

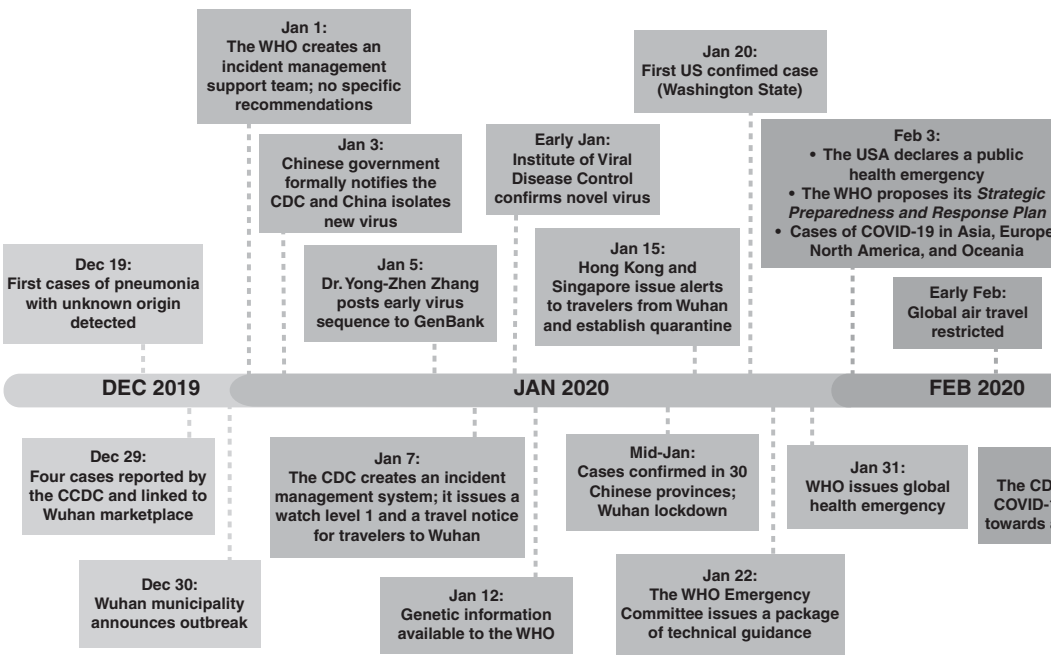

Figure 1.2 Pandemic evolution: from early detection to the declaration of the COVID-19 pandemic.
CCDC, Chinese Center for Disease Control and Prevention; CDC, US Centers for Disease Control and Prevention; WHO, Wor

Local authorities responded by initiating virus-typing studies, implementing population isolation, and closing the market. While most patients were linked to the Wuhan market, it soon became evident that human-to-human transmission had been occurring since mid-December and that the number of cases was doubling every 7.4 days.

Early reports referred to the outbreak as "viral pneumonia," suggesting that bacterial agents had been ruled out. Although the exact virus that caused the outbreak was unknown, the similarity in symptomatology to the previous SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks led health officials to hypothesize that it was another SARS-CoV outbreak.

Initially, Chinese health officials were free to share information about the newly emerging infectious disease; however, China's federal authorities quickly began inhibiting global medical and scientific communication. The Chinese government began to censure doctors who, in December 2019, raised the alarm about this pneumonia of unknown origin. For example, at the Central Hospital of Wuhan, a young ophthalmologist expressed his concerns to coworkers about a virus that he felt resembled SARS-CoV, a disease that originated in China and spread to four countries in 2003. The police summoned and admonished him, together with seven other doctors, on January 3, 2020. He was instructed to "stop making false comments" and investigated for "spreading rumors."[3] Tragically, he contracted COVID-19 and, on February 7, 2020, he passed away at the age of 33.[4]

By January 1, 2020, according to the World Health Organization (WHO) Newsroom, "the causal agent had not yet been identified or confirmed."[5] Further requests were made to the Chinese authorities for information that would enable assessment of the risk posed by the virus. On the same day, the Wuhan South China Seafood Market was closed, and the Chinese National Health Commission set daily meetings to monitor potential pneumonia epidemics. While it was clear that humans were infected with pneumonia of unknown etiology, the initial theories seemed to suggest a link to a wholesale fish and live animal market, indicating possible exposure to animals. Up to this point, information about the situation was only reaching local and international communities informally or through news released by the press, and they had received limited information to determine and monitor the potential risks.[3,5] The WHO assembled an incident management support team, which recommended continued public health measures and surveillance of influenza and severe acute respiratory infections. These recommendations did not include any specific measures for travelers.

On January 3, 2020, the Chinese government formally notified the director of the US Centers for Disease Control and Prevention (CDC) of the outbreak, revealing that 44 patients with pneumonia of unknown etiology had been reported, 11 of whom were critically ill, with the remaining 33 in stable condition.[3, 6] In January 2020, Chinese scientists at the National Institute for Viral Disease Control and Prevention announced the discovery of a new coronavirus.[7] This novel coronavirus was the pathogenic cause of the viral pneumonia of unknown etiology, designating the disease as a novel coronavirus-infected pneumonia.

Responding to a surge in pneumonia cases with unknown etiology, on January 7, 2020, the CDC established an "incident management system" and issued watch level 1 travel precautions for Wuhan, China. The CDC recommended that visitors to Wuhan avoid contact with sick people; avoid animals (alive or dead), animal markets, and products that originated from animals (such as undercooked meat); and wash their hands often with soap and water. Additionally, the CDC advised anyone who had traveled to Wuhan and felt sick

to isolate at home, except when seeking medical attention. At this stage, the WHO was uncertain of the cause of the 59 pneumonia-like cases, but it began to suspect that a novel coronavirus was to blame. Further research was required to correctly diagnose the individuals infected with the emerging virus.

Viral Pathogen Sequencing

Genomic sequencing is a laboratory technique used to decipher the full genetic composition of an organism (a virus in this case) or cell type. This approach may also be used to detect changes in specific regions of the genome. Viral sequencing was a quickly emerging technology that was critical in the diagnosis of COVID-19 and for understanding the transmission and management of the novel coronavirus.

On January 5, 2020, researchers at Fudan University, Shanghai, at the Shanghai Public Health Clinical Center and at the Fudan University School of Public Health published the sequence of SARS-CoV-2, the virus that causes COVID-19.[8, 9] The sequence was published to GenBank and the Global Initiative on Sharing All Influenza Data, both of which are online databases that are open and accessible to the public.

The genetic information became available to the WHO on January 12, 2020, opening the gateway for laboratories in different countries to produce specific, diagnostic polymerase chain reaction (PCR) tests that could detect the novel infection. The isolation and sequencing of the new virus confirmed it was a coronavirus.[10] While the Chinese researchers provided an essential tool for developing diagnostic tests, the Chinese authorities reacted negatively once again, closing the sequencing laboratory and ordering the "rectification" of disclosed statements on the virus, as well as the censorship of "misleading information" on social media.[3]

Assessment of Infectivity

In early January 2020, the Wuhan Municipal Health Commission stated that there was "no clear evidence of person-to-person transmission and while the possibility of limited person-to-person transmission cannot be ruled out, the risk of sustained person-to-person transmission was low."[11] A retrospective analysis of initial data shows that this was not true, the data highlights the necessity for early assessments of disease infectivity. Assessments of disease infectivity provide vital insight into how easily a disease is transmitted from human to human, which better informs officials on the best mitigation practices. Finally on January 20, 2020, China confirmed person-to-person transmission of the novel coronavirus and infections among medical workers.[3]

A universal measurement of disease transmission is the reproduction index (R_0). The R_0 index is defined as the number of susceptible people that one person with the disease can infect. It is a function of the following variables: the period of infectivity after infection, the chance of infection transmission per contact between a susceptible and an infectious individual, and the contact rate.[12]

Studies found that the initial Wuhan SARS-CoV-2 strain exhibited an estimated R_0 value between 1.4 and 2.5. For context, this value is displayed in Table 1.1 in comparison with other coronaviruses and known respiratory viral diseases with potential epidemic spread.[13] It is important to note that the infectivity of SARS-CoV-2 changed with the introduction of new variants.[14–16] Each variant presented structural changes to the viral spiral proteins that control binding to epithelial angiotensin converting enzyme 2 (ACE2) receptors and thus affect the infectivity of the virus. For more information on the impact of variant infectivity, see Chapter 9.