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CHAPTER

1

Overview of coronavirus pandemic

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1.1 Emergence and transmission of severe acute respiratory syndrome-Coronavirus-2

1.1.1 Introduction

In December 2019, several cases of pneumonia of unknown etiology were known in Wuhan, Hubei province, China. Many of these patients came from workers and people who lived near the Huanan Seafood Market, so the Chinese authorities establish the origin of the infection in this place (Lu et al., 2020).

It is reported that these patients developed a medical condition consisting of fever, cough, shortness of breath, and fatigue. Other symptoms they presented, but less frequently, were rhinorrhea, headache, sore throat, and gastrointestinal symptoms such as diarrhea and vomiting. They can also develop alterations in smell such as hyposmia or anosmia and taste such as dysgeusia. Fortunately, the majority of patients develop a mild curse of the disease but many patients were found that progressed rapidly to acute respiratory distress syndrome (ARDS) and respiratory failure requiring hospitalization and later they may develop other complications such as cardiovascular, kidney, and liver, in addition to cellular immunodeficiency, activation of coagulation and secondary bacterial infection that required admission to Intensive Care Units (ICUs) (Huang et al., 2020).

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Due to these clinical and epidemiological findings, the Chinese authorities were on alert in the search and isolation of the causative etiological agent. On January 7, 2020, the causative agent of the disease was identified as a new Coronavirus by the Chinese Centers for Disease Control and Prevention (CDC). Therefore the World Health Organization (WHO) announced the existence of a new Coronavirus disease-2019 (COVID-19) and published a comprehensive set of technical guidance on how to detect, manage cases and perform laboratory tests as well as recommendations on prevention and control of infections. It is intended to protect the population and exposed healthcare system (Timeline: WHO's COVID-19 response, 2021).

Analyzing the phylogenetic relationships and the genomic structure of the COVID-19 virus, it was determined that it belonged to the *Coronaviridae* family, *betacoronaviridae* genus, which has a great genomic similarity with the sequences of severe acute respiratory syndrome-related Coronavirus (SARS-CoV), specifically 80% and with the Middle East respiratory syndrome (MERS), specifically 50%. These similarities led the Coronavirus Study Group of the International Committee on Taxonomy of Viruses to term the virus as SARS-CoV-2 (de Groot et al., 2013).

From the pathophysiological and epidemiological points of view, it is important to establish the causes and consequences that this pandemic has generated over time. It has been observed that certain external and internal factors produce a worse evolution and therefore greater severity of the disease. All of this differentiates COVID-19 from other viruses and other pandemics. The study of these factors will help us to understand and optimize better forms of treatment that change over time and new prevention policies that will be discussed later.

In addition, the evaluation of the epidemiology, transmission routes, and the way in which it has been distributed by the different world public regions, is essential to implement a global response with different health measures that have been taken by the different countries to stop the advance of the disease and deal with the virus.

In this chapter, we are going to address all these issues divided into three parts: (1) Emergence and transmission of SARS-CoV-2, (2) Epidemiology of case-fatality rate and mortality, and (3) Global response to manage.

1.1.2 Genomic structure

SARS-CoV-2 is made up of a single-stranded RNA virus, with a diameter of 60−140 nm in size and a genome of 29,891 nucleotides that encodes for 9860 aminoacids (Chan et al., 2020). This encodes for 16 nonstructural proteins and four major structural proteins. Each structural protein includes the spike protein, the envelope protein, the membrane protein, and the nucleocapsid proteins.

The entry receptor for the virus is angiotensin-converting enzyme 2 (ACE2), which is widely expressed in a wide variety of cells, including the respiratory epithelium, monocytes, and alveolar macrophages, as well as in the tissues of the myocardial, liver, kidney, or gastrointestinal parenchyma. SARS-CoV-2 can also use CD209L and CD147 as alternative receptors but with a much lower affinity, which allows and explains a high rate of infectivity even in cells expressing a low level of ACE2 (Chan et al., 2020).

FIGURE 1.1 Genome of SARS-CoV-2. Composed of two open reading frames (ORFs): ORF1a and ORF1b that encode nonstructural proteins. The sgRNA encodes structural proteins, viral spike protein (S), membrane protein (M), an envelope protein (E), nucleocapsid protein (N), and other accessory proteins (3rd, 7th, 7b, 10).

The S protein mediates the binding of SARS-CoV-2 to ACE2 on the host cell which leads to virus entry and pathogenesis. After fusion of the viral envelope to the host membrane, the viral RNA is released into the cytoplasm. SARS-CoV-2 RNA is replicated through transcription of a minus-strand template and then generate 6−9 subgenomic mRNAs (sgmRNAs) leading to the translation of accessory and structural proteins of subsequent open reading frames (ORFs) (Wang et al., 2020; Zhu et al., 2020), as shown in Fig. 1.1.

These structural proteins are necessary to complete a viral replication cycle, and their translation from sgmRNAs (Zhu et al., 2020). Both genomic and subgenomic RNAs are produced through negative-sense intermediates RNA-dependent RNA polymerase. The nucleocapsids of the virus are assembled with the genomic RNA encapsulated in N protein in the cytoplasm. Nucleocapsid assembled in the endoplasmic reticulum-Golgi intermediate compartment and the complete mature virion is released from the cell through exocytosis (Alturki et al., 2020). The genomic structure and their principal receptors are shown in Fig. 1.2.

1.1.3 Transmission

Various Coronaviruses are known that infect animals and humans. Animals are a reservoir of the virus that can be transmitted to humans causing disease outbreaks. Around 15%−30% of common colds are known to be caused by different types of Coronaviruses. For example, the SARS-CoV outbreak in 2002 had its origin in bats in China and the MERS outbreak in 2012 had its reservoir in dromedaries, although it is also possible that it was transmitted from bats in the Middle East (Muralidar et al., 2020).

Therefore although the origin of the SARS-CoV2 outbreak is not exactly known, it could go back and have its initial focus on some of the animals in the Huanan Seafood market, such as bats, pangolins, and snakes (Ji et al., 2020; Li et al., 2005; Liu et al., 2019). These animals are believed to be the reservoir for the virus and it was subsequently transmitted to humans as the main transmission mechanism (Ji et al., 2020; Li et al., 2005; Liu et al., 2019).

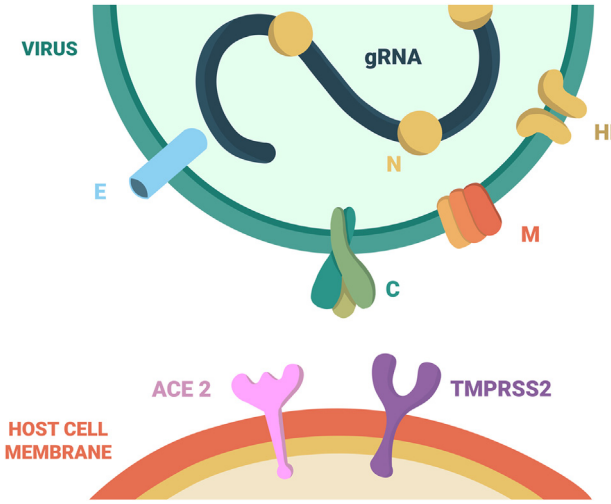

FIGURE 1.2 Genomic structure and receptors. Enveloped pleomorphic particle-containing single-stranded RNA packaged in a nucleocapsid (N). The envelope contains major surface antigens such as hemagglutinin-esterase (HE), and the spike protein trimer (S), which surrounds RNA. This virus requires transmembrane serine protease 2 (TMPRSS2) to cleave protein S, which allows targeting and binding of the angiotensin-converting enzyme receptor 2 (ACE2), followed by endocytosis of the virus.

However, other studies concluded that it was possible transmission between humans since many SARS-CoV-2 cases had not visited the market and had been in close contact with other infected, even before suffering symptoms of the disease (Carlos et al., 2020). Therefore it was shown that people can transmit the virus even in an asymptomatic state. There are many ways in which the virus can be transmitted person-to-person, either through direct contact or through droplets when a person sneezes (Morawska & Cao, 2020).

Different studies were carried out to evaluate the stability of the virus in different environments and on different surfaces, observing that SARS-CoV-2 remained viable for 3 hours in aerosols, 4 hours on copper, 24 hours on paper and cardboard and 72 hours on stainless steel and plastic surface (Van Doremalen et al., 2020).

The severity level of the SARS-CoV-2 disease is lower compared to SARS-CoV and MERS, but the range of infectivity is much higher than other Coronaviruses, probably due to its viral spread, the incubation period, and binding force to its ACE2 receptor. This infectivity is more similar to the influenza virus and reaches its highest level shortly or before the onset of symptoms, this rapid spread of the virus begins 2–3 days. Subsequently, the viral load decreases significantly after the onset of symptoms (He et al., 2020).

Because asymptomatic people can transmit the virus and the pandemic situation has continued to grow throughout the world, it is difficult in many regions to carry out adequate isolation and quarantine period. For this reason, the development of vaccines that help prevent the spread of the disease has been of vital importance since we do not have an effective treatment against the disease (Alturki et al., 2020; Varghese et al., 2020).

The number of COVID-19 cases reported by the WHO has been increasing since the first report in December 2019 by the WHO China office (WHO Novel Coronavirus 2019-nCoV Situation Report -1, 2020a). The infection began to spread from the Huanan Seafood Market in Wuhan, while the exact route from the first case remains unknown. Initially, the number of cases began to grow until February and subsequently gradually decreased at the beginning of March 2020 in China thanks to the greater knowledge of the disease and the best-standardized way of diagnosis, treatment, and isolation (Ahn et al., 2020; Lu et al., 2020).

The first case of Coronavirus reported by the WHO outside of China was in Thailand on January 13, 2020. In the early stages of the global spread of the disease outside of China, the reported cases were due to travelers who have been infected in China and later traveled to other regions outside, spreading the disease and consequently generating new outbreaks of COVID-19. Some of the countries that reported travel-associated COVID-19 cases were Thailand, Japan, the Republic of Korea, Taiwan, the United States, Hong Kong, Macao, Vietnam, Singapore, Malaysia, Australia, Canada, France, and Germany represented in Fig. 1.3. Subsequently, it began to spread to other Asian and European regions such as South Korea, India, Spain, or Russia from the end of January and February 2020 (Coronavirus disease 2019 COVID-19: Situation Report – 26 (15 February 2020)—China, 2020). In March, cases were still being reported in more than 170 countries around the world, so due to the rapid expansion of the virus, on March 11, 2020, the COVID-19 disease was declared a pandemic by the WHO. A few days later, specifically on March 15, 153.517 laboratory-confirmed COVID-19 cases had already been reported with approximately 5.735 deaths (WHO Novel Coronavirus 2019-nCoV Situation Report - 55, 2020b).

One year later, in March 2021, the number of laboratory-confirmed reported cases was 126.890.643 and the total number of deaths was 2.778.619 worldwide (Weekly epidemiological update on COVID-19, (30 March 2020), 2021). The increase in the number of cases and mortality has caused changes in all aspects of our daily lives. From changes in the way, we relate to other people to changes in the way of working, implanting teleworks in many areas, as well as when investing our free time doing sports. It constitutes one of the first pandemics in the era of technology and social networks and it is mandatory to promote the best practice to protect each other.

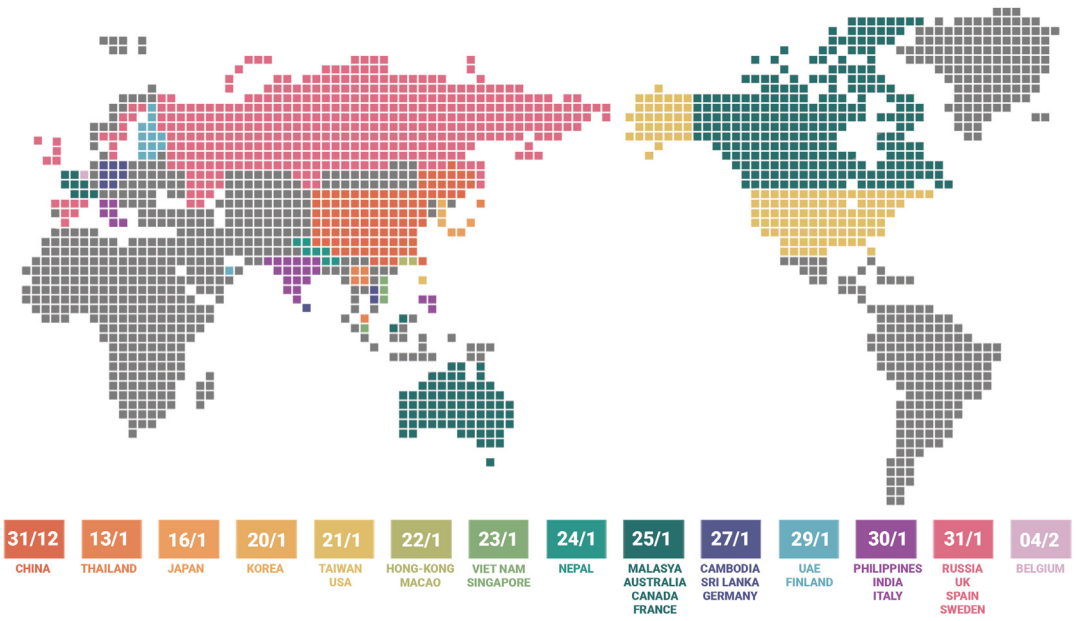

FIGURE 1.3 COVID-19 distribution. Expansion of the SARS-CoV-2 by the different countries during the first month.

1.2 Case-fatality rate and mortality

1.2.1 Case-fatality rate and infection-fatality rate: introduction

Many different public health and epidemiological studies have been published since SARS-CoV-2 infection and COVID-19 outbreak (Centers for Disease Control & Prevention, 2021). These studies have covered a numerous range of disciplines, including medicine, mathematics, physics, and social sciences, which has led to an important amount of information that sometimes is as valuable and interesting to public health policies as difficult to assess with certainty. Two of the most useful measures are COVID-19-related fatality rates (those that relate the number of cases to mortality): Case-fatality rate (CFR) and infection-fatality rate (IFR). Both are indicators of the virulence or severity of disease (Boseman, 2014; Meyerowitz-Katz and Merone, 2020; Oke and Heneghan, 2020)

1.2.2 Case-fatality rate and infection-fatality rate: definitions

1.2.2.1 Case-fatality rate

CFR is usually calculated as the number of total confirmed deaths due to a disease divided by the number of total confirmed cases for a particular period (i.e., a year). As a rate, it reflects the dynamic of the fatality over time among cases that are diagnosed. These studies are easier to calculate because of its availability of data: Most of the world's governments provide information on the number of diagnosed cases and total deaths due to a specific disease, and there are different official sources available on the internet where those data can be examined (Boseman, 2014; Meyerowitz-Katz & Merone, 2020; Oke & Heneghan, 2020; Our World in Data, 2021) (Box 1.1).

CFR is not constant. As a time depending-rate, it can vary over time and between populations, depending on the interplay between the three sides of a triangle: the agent that causes the disease, the host of the disease, and the environment surrounding all the processes. The environment concept includes both the physical components (e.g., geographical and climatic differences between countries) and the sociocultural components (including economic resources, public health policies, or the cultural way of life) (Boseman, 2014).

BOX 1.1

Example calculation 1:

100 people in a community of 1000 people are diagnosed with a certain disease in a month, and 15 of them die from the effects of the disease, the CFR would be 0.15.

It is important to keep in mind that if some of the cases have not yet been resolved (neither died nor fully recovered) at the time of analysis, a later analysis should include additional deaths and arrive at a higher number of the CFR.

To say an example, the CFR can increase if a microorganism needs a certain temperature to reproduce, and due to climate change, that organism is now available to live in new zones where it could not arrive before. That is what has happened with the *Aedes albopictus* mosquito in Western Europe, the transmitter of yellow fever, dengue, and other virus diseases. In another example, CFR may increase if the healthcare system is overwhelmed by the sudden increase of cases of a pandemic, which would lead to a depletion of health resources and worse patient care standards.

1.2.2.2 Some other terms sometimes related to case-fatality rate

CFR is sometimes confused with other terms that are also important to understand because although similar, they hide some differences that are remarkable to be aware of and not be misled.

The mortality rate (or death rate) is a measure of the relative number of deaths from a given cause (in this case, due to COVID-19), within the entire population that it has been studied per unit of time (i.e., a year). In contrast, CFR applies only to diagnosed cases (Box 1.2).

The case-fatality ratio is a comparison between two different case-fatality rates expressed as a ratio. It can compare two CFRs of two different diseases (usually the most killer goes first) or can be used to assess the impact of an intervention or treatment, comparing CFR before and after the intervention (Box 1.3).

BOX 1.2

Example calculation 2:

In our 1000 people community with 100 people diagnosed with the disease in a month, and 15 of them dying from the effects of the disease, the mortality rate would be 0.015.

BOX 1.3

Example calculation 3:

If we got an "A" disease with a CFR of 0.15 and a "B" disease with a CFR of 0.03, the case-fatality ratio would be A/B = 0.15/0.03 = 5.

If we got an "A" disease with a CFR of 0.15 (A1) and after a certain intervention the CFR decreases to 0.05 (A2) the case fatality ratio would be A1/A2 = 0.15/0.05 = 3 when comparing untreated and treated groups.

1.2.3 Some special considerations and limitations

Despite the fact that there are considerable official sources with the necessary data to calculate these measures, it is not always easy to compare studies between different populations due to methodological differences between them. It should be bear in mind that the CFR will depend on the number of cases that are diagnosed and therefore it will rarely refer to the total number of actual cases of the disease because it will depend on how many people consult for their symptoms and are properly diagnosed (Ioannidis, 2021).

In addition, not all deaths from disease are always confirmed, but sometimes probable or possible deaths are included, so the variation between different studies, even within the same population, can be great. There are consequently other measurements that will try to approximate the number of deaths to the total number of cases, such as the IFR.

1.2.4 Infection-fatality rate

IFR represents the proportion of deaths among all infected individuals, including all asymptomatic and undiagnosed subjects, and due to the difficulty in knowing the diagnosed nonasymptomatic cases, it may be inferred. The IFR aims to estimate the fatality rate in both sick and healthy infected and in both detected/tested and undetected/untested cases. Therefore it may be noted that the IFR cannot exceed the CFR, because it adds more cases to its denominator (Boseman, 2014).

Calculating IFR is far more complicated than CFR because it needs to extrapolate to the proportion of all infected individuals. Generally, the estimation of cases can be done through survey studies in which participants undergo a seroprevalence test or another validated diagnostic technique, or with mathematical models based on the mobility of known cases.

1. Most of the medical papers published use seroprevalence (measuring specific antibodies of an infectious disease) in the general population, or in samples that might approximately represent the general population to infer the number of total individuals. Using seroprevalence studies implies considering that the total number of antibodies we measure is influenced by the validated test we perform: its sensitivity and specificity, as well as the window period that passes until the antibodies, can be detected and the time they last in the body before they disappear and cannot be measured anymore (Pastor-Barriuso et al., 2020).
2. Other publications that do not use seroprevalence studies work with mathematical models that estimate infection rates from possible relationships and contacts between infected individuals and susceptible individuals in a region (network transmission models). They use four-possible variables of individuals including susceptible, exposed, infectious, and removed (recovered or deceased) individuals and data on the mobility of individuals in the region (counts of visitors to locations in each zip code based on mobile device locations) to develop mathematical equations that construct the model (Yang et al., 2021). These studies, on the other hand, can vary more and be more difficult to interpret depending on the variables that the mathematical model takes into account.

1.2.5 Case-fatality rate and infection fatality rate in Coronavirus disease 2019

Taking all this into account, we can understand the complexity of the studies that address issues related to fatality rates in the midst of an environment as adverse as the onset of a new infectious disease that has become a pandemic.

As it is shown in different studies, mean and median COVID-19 CFR worldwide are near to 3% and 2%, respectively (Oke & Heneghan, 2020), with the highest rates found in Yemen (27%), West and North Europe (15%), and North America (10%) (Centers for Disease Control & Prevention, 2021)

The median infection fatality calculated from different studies of serologic prevalence varies from 0.00% to 1.63% but is mostly estimated between 0.27% and 0.9%. On the other hand, network transmission models from cities of the United States are less optimistic and approximate the IFR to 1.39% (Yang et al., 2021). European studies approximate it to 0.83%−1.07% (Pastor-Barriuso et al., 2020). Systematic reviews and *meta*-analysis calculate the IFR value in 0.68% (0.53%−0.82%) with data from the mid-2020 year (Levin et al., 2020; Meyerowitz-Katz & Merone, 2020).

1.2.5.1 Special considerations with Coronavirus disease 2019 fatality rates

COVID-19 has a clear degree of age. Thus in Western countries, the majority of deaths have occurred in residences. But in these countries, have low rates among nonelderly, non-debilitated people. IFR increases by age, from 0.005% for children to 0.4% at age 55, 1.4% at age 65, and 15% for ages 85 and above. This upward trend in percentages can be found similarly with the CFR, from 1.3% at age 55, 3.6% at age 65, and 8% at age 70 (Kavaliunas et al., 2020; Levin et al., 2020; Public Health Agency of Sweden, 2020; Seoane & Tu, 2021).

In addition, people with an underlying health condition have a much higher fatality rate than those without. In the group of people with Covid-19 and some cardiovascular disease, more than 10% died. Diabetes mellitus, chronic respiratory diseases, hypertension, and cancer are all well-recognized risk factors. By comparison, the CFR is more than 10 times lower (0.9%) for people without any preexisting health condition (Cao et al., 2020; Ioannidis, 2021; Ritchie & Roser, 2020; Unger, 2021).

Within the age ranges, men tend to have twice the risk than women (in the large Spanish seroprevalence study, 1.14% versus 0.58% values that are similar to other studies) (Pastor-Barriuso et al., 2020). Some authors speculate that the higher mortality in men could result from more health comorbidities than in women, and also differences in cellular immunity between men and women (including poorer T cell activation and an increase in proinflammatory cytokines in men) (Català et al., 2021; Levin et al., 2020; Seoane & Tu, 2021).

There are also differences in geographic (lower rates have been found in Asian countries) and economic distribution. It has been estimated that the overall CFR for the high-income countries would be 5.0%, compared with a CFR of 2.8% for low-income countries. The upper-middle-income countries would show a CFR of 4.3%, while the lower-middle-income countries stand at 3.7%. Different factors have been studied (younger population, previous exposure to other Coronaviruses that provides immunity, genetic differences, hygiene etiquette, lower infectious load, etc.) without reaching a clear conclusion: probably, having a young population influences, but on the other hand, comorbidities, poverty,

TABLE 1.1 Estimated case-fatality rate of other pandemic and epidemic diseases.

Disease	Case-fatality rate (CFR)
SARS-CoV	10%
MERS-CoV	34%
Seasonal flu (US)	0.1%–0.2%
Ebola	40%–50%

Based on OurWorldInData.

frailty malnutrition, and congested urban living may have an adverse effect on risk that may increase both rates (Ioannidis, 2021; Shah et al., 2021).

Also, it is important to remember that these measurements are not static. Since CFR and IFR are time-dependent rates, they can be influenced and modified by different measures. Specific political and public health decisions that change over time, the dynamics between communications and the mobility of people in places, the use of empirical treatments in the absence of sufficient scientific evidence replaced by the studies that are emerging, are some examples of how the rates can vary over time (Borges do Nascimento et al., 2020; Burki, 2020; Callejas Rubio et al., 2020; COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 COVID-19 Treatment Guidelines, 2021; Trilla, 2020; Wu & McGoogan, 2020).

Considering this, the overall COVID-19 infection-fatality risk estimated is about 10 times larger than that for seasonal influenza (Table 1.1).

The high fatality risk in the elderly and other specific groups supports the different existing political measures and public health campaigns to shield these groups from infection. Knowing these rates and their evolution over time can help us understand whether the different measures and political decisions are useful to slow the advance of the pandemic (COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 COVID-19 Treatment Guidelines, 2021; Kavaliunas et al., 2020; Pastor-Barriuso et al., 2020; Perlman, 2020; Sreedharan et al., 2021; Thompson et al., 2003; Trilla, 2020; Unger, 2021; Wu & McGoogan, 2020).

1.3 Global response to manage

1.3.1 State of the art

The outbreak of a new infectious disease drove a quick global response whose main elements were coordinated by WHO, which started assessing from January 15th the clinical and sociological management based on expert's agreements. Alerts appeared on December 19th, and since then WHO performed global advice at different levels:

1. operational planning guidelines;
2. weekly briefings updates;
3. supporting research response and transparency on clinical essays and vaccine development tools access to information; and
4. leadership for coordination national donors and manufacture at a global scale.

Countries reacted at different paces and followed WHO's directives and recommendations depending on their transmission and fatality rates, and their capacity to isolate their population. Down the line, we are going to:

1. Review the different models of the Government's response from a global, national and institutional perspective.
2. Trace the therapeutic approaches and pharmacological measures that have been implemented since the emergence of COVID-19 disease.
3. Track the development of vaccines around the globe and the vaccination strategies used in different countries.

1.3.2 Institutional organization

1.3.2.1 Global response

WHO declared a Public Health Emergency of International Concern (PHEIC) on January 30th after two meetings held by the Emergency Committee. From then, WHO made various efforts to internationally coordinate the necessary support in the early steps of the Coronavirus pandemic. Global milestones are summed up in Table 1.2.

TABLE 1.2 Global milestones on Coronavirus disease 2019. A timespan focused on major events in 2020 that marked the evolution of COVID-19. Main actions on information, funding, and scientific landmarks taken by the WHO and its collaborators are summed up in chronologic order. Data adapted from Timeline: WHO's COVID-19 response.

Date	Event
January 1st	WHO requested information on the *reported cluster of atypical pneumonia cases in Wuhan* from the Chinese authorities. WHO activated its Incident Management Support Team (IMST).
January 9th	*WHO reported that Chinese authorities have determined that the outbreak is caused by a novel Coronavirus.*
January 13th	WHO publishes *first protocol for an RT-PCR assay* by a WHO partner laboratory to diagnose the novel Coronavirus.
January 14th	WHO held a press briefing during which it stated that, based on experience with respiratory pathogens, *the potential for human-to-human transmission* in the 41 confirmed cases in the People's Republic of China existed: "it is certainly possible that there is the limited human-to-human transmission." WHO tweeted that preliminary investigations by the Chinese authorities had found "no clear evidence of human-to-human transmission." In its risk assessment, WHO said the additional investigation was "needed to ascertain the presence of human-to-human transmission, modes of transmission, a common source of exposure and the presence of asymptomatic or mildly symptomatic cases that are undetected."
January 20–21st	WHO conducted the first mission to Wuhan and met with public health officials to learn about the response to the cluster of cases of novel Coronavirus. The United States of America reported its first confirmed case of the novel Coronavirus. This was the *first case in the WHO Region of the Americas.*
January 24th	France informed WHO of three cases of novel Coronavirus, all of whom had traveled from Wuhan. These were the *first confirmed cases in the WHO European region.*

(*Continued*)

TABLE 1.2 (Continued)

Date	Event
January 30th	The Director-General *declared the novel Coronavirus outbreak a public health emergency of international concern (PHEIC)*, WHO's highest level of alarm.
February 3rd	WHO finalized its Strategic Preparedness and Response Plan (SPRP), centered on improving capacity to detect, prepare and respond to the outbreak.
February 11th	*WHO announced that the disease caused by the novel Coronavirus would be named COVID-19*.
February 24th	The Team Leaders of the *WHO-China Joint Mission on COVID-19 held a press conference to report on the main findings of the mission*. The Mission warned that "much of the global community is not yet ready, in mindset and materially, to implement the measures that have been employed to contain COVID-19 in China." The Mission stressed that "to reduce COVID-19 illness and death, near-term readiness planning must embrace the large-scale implementation of high-quality, nonpharmaceutical public health measures," such as case detection and isolation, contact tracing and monitoring/quarantining, and community engagement. Major recommendations were developed for the People's Republic of China, countries with imported cases and/or outbreaks of COVID-19, uninfected countries, the public, and the international community. For example, in addition to the above, countries with imported cases and/or outbreaks were recommended to "immediately activate the highest level of national *Response Management protocols to ensure the all-of-government and all-of-society approach needed to contain COVID-19*." Success was presented as dependent on fast decision making by top leaders, operational thoroughness by public health systems, and societal engagement. In addition to the Mission press conference, WHO published operational considerations for managing COVID-19 cases and outbreaks onboard ships, following the outbreak of COVID-19 during an international voyage.
March 3rd	*WHO issued a call for industry and governments to increase manufacturing by 40% to meet rising global demand* in response to the shortage of personal protective equipment endangering health workers worldwide.
March 9th	*The Global Preparedness Monitoring Board*, an independent high-level body established by WHO and the World Bank, responsible for monitoring global preparedness for health emergencies, called for an *immediate injection of US$8 billion for the COVID-19 response*.
March 18th	*WHO and partners launched the Solidarity trial*, an international clinical trial that aims to generate robust data from around the world to find the most effective treatments for COVID-19.
March 21st	In light of many Member States facing shortfalls in testing capacity, WHO published *laboratory testing strategy recommendations for COVID-19*.
March 26th	The Director-General addressed the *Extraordinary G20 Summit on COVID-19*, chaired by King Salman of Saudi Arabia, and called on G20 leaders to fight, unite, and ignite against COVID-19.
March 31st	WHO published a Scientific Brief on the off-label use of medicines for COVID-19, addressing the issue of compassionate use.
April 2nd	WHO reported on *evidence of transmission from symptomatic, presymptomatic, and asymptomatic people infected with COVID-19*, noting that transmission from a presymptomatic case can occur before symptom onset.
April 4th	WHO reported that over 1 million cases of COVID-19 had been confirmed worldwide, a more than tenfold increase in less than a month
April 7th	WHO issued a document outlining what the health sector/system can do to address COVID-19 and violence against women. WHO finalized practical considerations for religious leaders and faith-based communities in the context of COVID-19.

(*Continued*)

TABLE 1.2 (Continued)

Date	Event
April 13th	WHO published a statement by 130 scientists, funders, and manufacturers from around the world, in which they committed to working with WHO to speed the development of a vaccine against COVID-19.
April 16th	WHO issued guidance on considerations in adjusting public health and social measures, such as large-scale movement restrictions, commonly referred to as "lockdowns."
May 7th	The UN launched an update to the Global Humanitarian Response Plan for $6.7 billion to minimize the most debilitating effects of the pandemic in 63 low and middle-income countries.
May 18–19th	The 73rd World Health Assembly, the first-ever to be held virtually, adopted a landmark resolution to bring the world together to fight the COVID-19 pandemic, cosponsored by more than 130 countries—the largest number on record—and adopted by consensus.
May 27–29th	The WHO Foundation was established, with the aim of supporting global public health needs by providing funds to WHO and trusted partners.4 Thirty countries and multiple international partners and institutions launched the COVID-19 Technology Access Pool (C-TAP), an initiative to make vaccines, tests, treatments, and other health technologies to fight COVID-19 accessible to all. Voluntary and based on social solidarity, C-TAP aims to provide a one-stop-shop for r equitably sharing scientific knowledge, data, and intellectual property.
June 5th	WHO published *updated guidance on the use of masks for the control of COVID-19*, which provided updated advice on who should wear a mask, when it should be worn, and what it should be made of.
July 15th	The COVAX Facility, a mechanism designed to guarantee rapid, fair, and equitable *access to COVID-19 vaccines worldwide, secured engagement from more than 150 countries, representing over 60% of the world's population*.
July 24th	WHO issued a *policy brief to prevent and mitigate the impact of COVID-19 across all aspects of long-term care*, including home- and community-based care.
September 22nd	WHO issued the **f***irst Emergency Use Listing for a quality antigen-based rapid diagnostic test* for detecting the SARS-CoV-2 virus, which causes COVID-19.
September 30th	The UN and partners welcomed nearly US$1 billion in new financing for the Access to COVID-19 Tools (ACT) Accelerator, from governments, private sector, civil society, and international organizations.
October 15th	*WHO announced conclusive evidence on the effectiveness of repurposed drugs for COVID-19*. Interim results from the Solidarity Trial indicated that remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients.
December 3–4th	The UN General Assembly held a special session (UNGASS) on the COVID-19 pandemic response, with discussions focused on equitable access to vaccines as well as socioeconomic impact and recovery, including financing to ensure no one is left behind. Speaking at the event, the Director-General called on world leaders to invest in: vaccines to end the pandemic, preparedness to prevent the next one, health as the foundation of peace and prosperity, and multilateralism to safeguard our common future.
December 15th	United Kingdom authorities reported a SARS-CoV-2 variant to WHO. The United Kingdom referred to the variant as SARS-CoV-2 VOC 202012/01.
December 31st	WHO issued *its first emergency use validation for a COVID-19 vaccine* and emphasized the need for equitable global access.

It is important to note how social and behavioral science has been needed to address this global health crisis, as reflected in WHO's brief reports: firstly, by understanding cultural influence on social norms and self-commitment. This aimed to an optimize management of threat and fear perception and limited discrimination. Secondly, for a correct management of the pandemic, a nonpolarized political approach together with the spread of accurate information of the pandemic was to be entailed to avoid separatism and the emergence of conspiracy policies, resulting in collaborating and community efficient approaches (Bavel et al., 2020).

1.3.2.2 National policies

Most countries have experienced three waves of COVID-19 cases by April 2021. In order to reduce community transmission, restrictions have been applied all around the world with different degrees of severity responding to epidemiological situations and relancing programs of the countries, consisting in fiscal measures such as loans to provide short-term support to affected businesses, direct subsidies to SMEs and businesses to help maintain their employees, grants to entrepreneurs and firms, lump-sum transfers to the vulnerable.

A comprehensive review of the policies carried out by each country can be consulted at the International Monetary Fund (International Monetary Fund, 2021). In most cases, regulations were entailed in these order:

1. Generalized lockdown, temporary closure of many businesses, border closure, suspension of schools, airports, and transportation hubs; social distancing, and disinfection of public spaces. Under which people were not allowed to leave their homes except for buying essential goods, attending medical appointments, or working in essential services.
2. Relaxed containment maintaining social distancing measures, mass gatherings banned, progressive workers reincorporation and reopening of retails.
3. Curfew dawn to dust, reopening of restoration, cultural and touristic attractions.

Mathematical modeling allows evaluating the suitability of national policies, as we will see further in this book. Asia-Pacific countries like China and Australia implemented effective containment measures and are expected to have a quick recovery as they vaccinate. An illustrative example of the efficacy of early-applied rigorous countermeasures is China's centralized policy, detailed in Box 1.4. Its rapid actions allowed the region to recover a social and economic activity within weeks, much before other regions of the globe that applied less strict containing measures (Burki, 2020). Nevertheless, the analysis should take account of confounding factors, such as the awareness of the population (who had faced a respiratory emergency in the last decade) and the low percentage of aged people living in care structures (3% compared to up to 8% in Europe or United States) (Rodrigues et al., 2012).

The efficacy of quarantine models can be also assessed in small environments as cruise ships. The COVID-19 pandemic spread to up to 40 cruise ships, with the nature of such ships—including crowded semienclosed areas, increased exposure to new environments, and limited medical resources—contributing to the heightened risk and rapid spread of the disease. The large-scale quarantine model implemented by the Japanese government at the very beginning of the global transmission is explained in Box 1.5.

BOX 1.4

China's policy, or how to strict healthcare policies are a major factor to prevent mortality.

After the identification of a new respiratory agent, a strict lockdown was applied in Wuhan, the first region to be hit by COVID-19; public transport was suspended, healthcare points were created and testing of 9 million habitants were launched within one month. Up to 16 spaces with the mass capacity we readapted to become hospitals ("Fangcangs") to treat and isolate the low to moderate cases of COVID-19 infection during this time. They hold 13.000 beds for a month and were no longer needed.

BOX 1.5

A large-scale quarantine model: the Diamond Princess, the first cruise to have a major outbreak on board.

Over 700 people became infected, and 14 people died. At the time, the ship accounted for over half the reported cases of SARS-CoV-2 outside of mainland China.

A large-scale quarantine model was implemented and all passengers including asymptomatic patients were tested for SARS-CoV-2 by using reverse transcription-polymerase chain reaction (RT-PCR). A total of 2666 passengers and 1045 crew members underwent RT-PCR testing, and passengers were asked to remain quarantined for 14 days in their cabins. Among 3,711 Diamond Princess passengers and crew, 712 (19.2%) had positive test results for SARS-CoV-2. Of these, 331 (46.5%) were asymptomatic at the time of testing. Among 381 symptomatic patients, 37 (9.7%) required intensive care, and nine (1.3%) died (Yamahata & Shibata, 2020). This experience occurring in a vulnerable environment to spread infection shows the crucial importance of quarantine for reducing transmission.

1.3.3 Healthcare approaches

The Coronavirus pandemic put healthcare systems under unprecedented stress to accommodate unexpected numbers of patients forcing a quick reorganization. Health ministries along with WHO recommendations gave the tips for a successful reorganization that was to be readapted to each structure, and many public-private partnerships were issued.

Most hospitals conducted a reorganization plan consisting of repurposing hospitalization wards and surgical rooms into isolation and critical care beds for COVID-19 patients. Many healthcare establishments created separated circuits for patients with respiratory symptoms, including a testing area separated from routine laboratory exams. These new

structures required rapid redeployment of medical staff and changing of scheduled activity, like for example, reducing elective surgery.

Although the adaptability of healthcare priorities has been crucial to cope with the pandemic, the burden of changing and delaying precedent objectives will have a substantial impact on patients and cumulative, potentially devastating, consequences for health systems worldwide. This can be seen at the Emergency Services, where patients resorted later than before resulting in advanced states of disease. Delaying time-sensitive elective operations, such as cancer or transplant surgery, may lead to deteriorating health, worsening quality of life, and unnecessary deaths. When hospitals resume elective activities, patients are likely to be prioritized by clinical urgency, resulting in lengthening delays for patients with benign but potentially disabling conditions where there may be less of a perceived time impact (COVIDSurg Collaborative, 2020).

Another area of healthcare severely impacted is mental health. The pandemic has had a direct impact as a psychological tool in the general population and specifically in people with mental disorders (particularly those with severe mental illness and cognitive impairment) and frontline workers. Healthcare systems have reacted to provide acute response, but some effects will probably remain (Moreno et al., 2020).

1.3.3.1 Therapeutics

The spectrum of medical therapies to treat COVID-19 is growing and evolving rapidly. Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of the disease, while immunosuppressive/antiinflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The main groups under consideration are multitarget antiparasitic (chloroquine and ivermectin), glucocorticoids, macrolide antibiotics, and antiviral drugs including their pharmacokinetic boosters. As of May 11th, up to 290 therapies have been investigated through randomized essays and seven in nonrandomized studies (Tarazona et al., 2021).

No therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression. The COVID-19 Treatment Guidelines Panel recommends providing supportive care and symptomatic management to outpatients with COVID-19; steps should also be taken to reduce the risk of SARS-CoV-2 transmission to others. Patients should be advised about when to seek in-person evaluation (Pan et al., 2021).

In outpatients with mild to moderate COVID-19 who are at high risk for disease progression, anti-SARS-CoV-2 antibody-based therapies may have the greatest potential for a clinical benefit during the earliest stages of infection. For these patients, it is recommended to administer bamlanivimab plus etesevimab (AIIa) or casirivimab plus imdevimab (AIIa), both of which are available through Emergency Use Authorizations (National Institutes of Health, 2021).

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest benefit observed in patients who require mechanical ventilation. Therefore the use of dexamethasone is strongly

recommended in this setting (Horby et al., 2021). Adding tocilizumab, a recombinant humanized antiinterleukin-6 receptor monoclonal antibody, to dexamethasone therapy was found to improve survival among patients who were exhibiting rapid respiratory decompensation due to COVID-19 (Tocilizumab in patients admitted to hospital with COVID-19 RECOVERY: preliminary results of a randomized, controlled, open-label, platform trial, 2021).

1.3.3.2 Vaccines

COVID-19 vaccines have been rapidly developed and distributed to help fight the pandemic. Delays in delivery is a main concern of governments as a large-scale vaccination is the only solution to overcome restriction policies.

As of May 2021, 15 vaccines have been approved among 118 candidates. Modern techniques have resulted in a variety of immunological approaches (viral vector, nucleic acid, attenuated, inactivated, and protein vaccines), all of them aiming to provoke an immunological reaction against a viral antigen. The targets and distribution of vaccine trials are shown in Fig. 1.4 (Chung et al., 2021).

After initial development, vaccines go through three phases of clinical trials to make sure they are safe and effective. During the development of COVID-19 vaccines, these phases have overlapped to speed up the process so the vaccines can be used as quickly as possible to control the pandemic.

Current discussions on updating existing vaccines to face SARS-CoV-2 variants are taking place, as there exists evidence showing a reduced response on vaccinated people to some variants. Genomic surveillance of SARS-CoV-2 variants has largely focused on mutations in S,

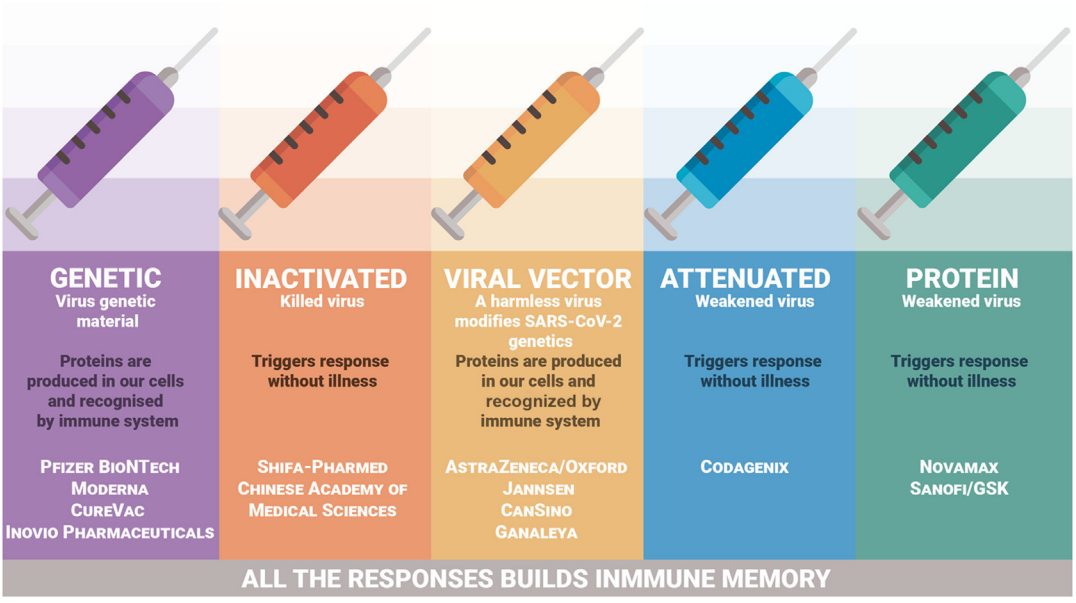

FIGURE 1.4 Main vaccines in development. Types and targets of vaccine trials.

which mediates attachment to cells and is a major target of neutralizing antibodies. There is intense interest in whether mutations in the spike glycoprotein mediate escape from host antibodies and could potentially compromise vaccine effectiveness since spike is the major viral antigen in the current vaccines. At this point, a strong selection of a variant at the population level is probably not driven by host antibodies because there are not enough immune individuals to systematically push the virus in a given direction. In contrast, if a variant has one or more mutations in a spike that increase transmissibility, it could quickly outcompete and replace other circulating variants. Because current vaccines provoke an immune response to the entire spike protein, it is hoped that effective protection may still occur despite a few changes at antigenic sites in SARS-CoV-2 variants (Lauring & Hodcroft, 2021).

1.4 Future perspectives

Even though the efforts made to coordinate a global scientific response since the emergence of COVID-19 have allowed a good understanding of the structure and transmission of SARS-CoV-2 at record-breaking speed; there are several gaps in knowledge that need to be filled.

The apparition of mutants with increased transmission ability and resistance to vaccines may compromise the global strategy based on rapid and massive vaccination of the population. However, the presence of a $3' \rightarrow 5'$ exonuclease that proofreads RNA products in transcription and replication in *Coronaviridae* family make believe that an universal vaccine may work against new strains, and thus the massive production of vaccines remains a crucial measure for long-term protection and even eradication of SARS-CoV-2. In the meantime, Private Protection Equipment with nose and mouth covering masks prevails as a strategy to reduce COVID-19 transmission.

There are different strategies proposed to boost host viral immunity. A comprehensive nutritional approach with supplementation in vitamins, zinc, and probiotics has been adopted as a complement to drug treatment bases in corticosteroids as it is believed to be one of the key regulators of the immune system. Other targets have been studied, like clinical trials with oral mTOR inhibitors (Mannick JB, Teo G, Bernardo P, et al.). The biology of aging with mTOR inhibitors to improve immune function in older adults: phase 2b and phase 3 randomized trials. *Lancet Healthy Longev*. 2021; 2: e250−e262. Further research on these fields is necessary to enhance protection against new emergent pathogens in an aging population, which has an increased susceptibility to viral infection. In this spirit, the development of broadly-reactive antiviral drugs appears as a priority to deal with emerging viruses.

A proactive strategy to deal with the challenge of emerging infectious diseases should be adopted, starting with a global network to track microbiological surveillance and coordinate the global response, promote cross-borders clinical trials to allow studies on different populations helped by the understanding of genomics.

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