1 Introduction

The single biggest threat to man's continued dominance on the planet is the virus.

Joshua Lederberg

Viruses populate the world between the living and the non-living, the molecules that can duplicate themselves and the ones that cannot. Inherent in the organization and properties of viruses are many of the secrets of life . . .

Arnold Levine

At the end of December 2019, an outbreak of pneumonia cases of unknown origin was reported in Wuhan, Hubei province, China. The patients presented with high fever and had difficulty breathing. Some, but not all, of these cases were in people who visited the Huanan Seafood Wholesale Market, where, in addition to seafood, a variety of live animals were also sold. Other infections occurred in people staying at a nearby hotel on December 23–27. All tests carried out by the Chinese Center for Disease Control and Prevention for known viruses and bacteria were negative, indicating the presence of a previously unreported agent. A new virus was isolated and its genome sequenced, revealing a similarity with SARS-like coronaviruses found in bats. Although very similar to the virus causing severe acute respiratory syndrome (SARS) in 2003, it was different enough to be considered a new human-infecting coronavirus. Clusters of infected families, together with transmission in medical settings, indicated that the virus had the ability to undergo human-to-human transmission. A month later, by the beginning of February 2020, the virus was found in several countries across the globe, and on March 11, 2020, the World Health Organization (WHO) declared it a global pandemic. The disease caused by the new coronavirus was called coronavirus disease 19, or COVID-19.

The rapid pace of these events led to significant confusion. Attitudes and perceptions in the population varied dramatically, from denial to serious concern and panic, mimicking the disparate comments and actions taken by public authorities and the media. After the declaration of the pandemic and the first serious outbreaks in Wuhan, Northern Italy, Spain, and Iran, it became clear that the emergence of this virus was a serious threat, and could lead to a significant overloading of healthcare systems. By the end of March 2020, the USA, the UK, India, and most countries in Europe had reported an escalating number of cases and deaths, and had implemented extensive public health measures, including lockdowns. The associated effects on the economy were daunting, including foreclosure of many businesses, escalating unemployment, international travel bans, market uncertainty, and significant reduction of demand for and production of goods and services, among many others.

Unfortunately, the confusion of the first few months of the pandemic led to a profusion of myths, large amounts of inconsequential information, and conspiracy theories that infected the Internet faster than the virus spread around the world. In trying to make sense of the situation, and to create a coherent narrative that incorporates the overwhelming data, many questions have arisen: questions about the nature of the virus and the disease it causes, about its changes, and about the future. This book addresses some of these questions. I have decided to structure the book in the form of a dialogue, of simple questions and answers. Most of these questions came from family, friends, and colleagues.

This book is aimed at the lay reader, one who has minimal knowledge of biology, virology, epidemiology, or medicine in general. I have tried to make the chapters self-contained, and they can be read in any order, although I recommend reading the first four chapters first, in order to get a clearer understanding of the biological and epidemiological concepts that are discussed in the chapters about specific viruses and outbreaks. Because this book is a short introduction to the topic, there are some important details that are overlooked. To compensate for the superficiality in how some themes have been treated, I have included at the end of the book a list of recommended reading material that will guide the interested reader to more in-depth treatment of specific topics. This material has been selected from among recent scientific journal papers of broader scope, and from textbooks. I would encourage the enthusiastic reader to follow up with these references. I apologize to some of the researchers whose work I have not been able to discuss or mention due to the introductory nature of this book.

Viruses are fascinating entities that awaken our deepest fears. The history of humankind is literally plagued with the narration of the devastating effects of infectious diseases, in which viruses have been major players. Smallpox killed one in every three people it infected, with an estimated 300 million deaths in the past century. The infamous Spanish Influenza of 1918 shocked the world with its rapid spread, completely overwhelming healthcare systems, and with its vicious attack on the young adult population. The human immunodeficiency virus (HIV) in the 1980s marked a then-young generation and challenged a rapidly evolving society. Rotavirus infection, a vaccine-preventable disease, is one of the most common causes of diarrhea in young children, and kills more than 100,000 children every year. Many other examples, recent and historical, easily come to mind.

Once an infectious pathogen appears, we would like to understand and quantify how it is spreading, what its effects are in the population, and how the efficacy of different public health measures can be evaluated. In the rapid expansion of the COVID-19 virus around the world, we have observed and experienced the role of drastic public health policies that have changed our social lives dramatically, and we have witnessed the rapid growth of cases and deaths associated with the disease. Chapter 2 deals with basic concepts in epidemiology – the science of evaluating the distribution of diseases and different control measures.

What do we know about the virus that causes COVID-19? The coronavirus disease, or COVID-19, is caused by the SARS coronavirus 2, or SARS-CoV-2. Chapter 3 explores viruses, and coronaviruses in particular. Viruses are the most common biological entity on Earth and are present in every realm of the surface of this planet. Only a very small fraction of them interact with humans, and only a small fraction of those are pathogenic. The pathogenic viruses, however, have captured most of the attention of the scientific community. Coronaviruses constitute a particular type of virus that can be found in

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mammals and birds. Some coronaviruses cause disease in humans, but most of them infect other species, such as bats, without apparent disease. Four coronavirus types are found commonly in humans and induce typical cold symptoms. Others can cause severe disease, like bronchitis in chickens or diarrhea in pigs. Some, as we have seen with the virus causing COVID-19, can cause severe disease in humans. Many questions come to mind. Is this a new virus? Where is it coming from? How does it relate to other coronaviruses? In the third chapter of this book I provide some basic notions of what viruses are, and describe coronaviruses in particular. I explain the different types of coronaviruses and where they can be found. All coronaviruses share a common but highly distinctive structure. I also briefly explain how they enter and leave infected cells.

How was the coronavirus that causes COVID-19 able to infect and spread in humans? To answer this question, we need to understand how viruses evolve. Viruses are the tiniest and most rapidly evolving biological entities known. Changes in viral genomes happen almost continually. All changes in viruses can be read in their tiny genomes, which keep all the information on the virus and its history. Reading genomes is like reading a history book, where the main characters are viruses. This record not only portrays the history, but also allows one to infer the rules of the processes that dictate the changes. Through the recent developments in genomic technologies, viral genomes can be sequenced rapidly and their changes can be observed almost in real time. As the COVID-19-causing virus spreads across the globe, we will be able to follow a parallel history by reading the genomes of the viruses collected in different parts of the world.

Chapter 4 explains the two main mutational mechanisms that drive the evolution of coronaviruses. The first one is what is known as the "sloppiness" of the replication machinery. Once a virus infects a cell, it makes tens of thousands of copies of itself. But these copies are sometimes (often) imperfect, with small variations on the main theme. Many times, these changes lead to a faulty copy. But sometimes, the new virus can acquire new abilities that become useful to the virus, such as the ability to enter a new type of cell or to evade recognition by the immune system of the organism it is infecting. But an even more dramatic mechanism is pervasive in coronaviruses: recombination. In a recombination event, two different viruses can swap genomic material rapidly, quickly acquiring new abilities. The combination of these two processes – sloppiness and recombination – shapes the evolution of coronaviruses. We will talk about these two mechanisms and how they can be read from viral genomes. Understanding how viruses evolve is far from an academic exercise: it will be fundamental to understanding the situation we are living in and what we have to do to be prepared.

Chapters 2–4 provide a background to contextualize the emergence of the virus that causes COVID-19, which is discussed in Chapter 5. Using genomic information, we relate the genome of the new virus, SARS-CoV-2, to other known viruses and where they were found. The new virus is related to SARS-CoV, the agent that caused the 2002–2003 SARS outbreak, and to many other viruses found in other species, mostly bats. I narrate the first known events in the history of this outbreak, how it was first identified, and how it has been evolving. I then discuss the disease caused by the virus – COVID-19 – its symptoms, and how it causes disease and death. I also devote some time to the demographics of the populations at risk, how it is affecting more men than women, and the effects on children.

Chapter 6 is devoted to the outbreak that occurred in 2002 and 2003 due to one of the closest relatives of the virus that causes COVID-19. That outbreak was SARS, and the virus was the SARS coronavirus, a close relative of SARS-CoV-2. These are the only two viruses in the same virus species that are known to have caused outbreaks in humans. There are remarkable similarities between the SARS outbreak of 2002–2003 and the COVID-19 outbreak in 2019–2020. The two viruses have many similarities in their genes, in the type of cells they infect, in how they enter cells, and in how they interact with the cell machinery and immune system. It is not surprising that the diseases caused by these two viruses share certain similarities. More interestingly, we can learn many things about the new virus causing COVID-19 from the work that scientists have carried out with the virus causing SARS. The basic biology and the clinically acquired knowledge from related viruses can help to accelerate the discovery of potential treatments for COVID-19.

Chapter 7 is a scientific misfit. It is about a virus, but not a coronavirus. Rather, it is about a virus that has been used widely as a comparison: influenza. The elements for comparison are obvious. Influenza causes respiratory diseases; it spreads through surfaces and air droplets in coughs and sneezes; and it causes severe disease in the elderly. These are all elements that are shared with

COVID-19. But, in many other aspects, the SARS-CoV-2 and the influenza viruses are very different, and the diseases caused by them, and the severity of those diseases, are very different. Most importantly, for seasonal influenza, there is at least partial immunity in the population, and we have vaccines and specific drugs for treatment. None of this is true for COVID-19. The lack of immunity to the COVID-19-causing virus has taken an immunologically unprotected population by surprise, leading to a dramatic surge in cases that has pushed healthcare systems to the verge of collapse. This rapid surprise attack has occurred in the past in the context of pandemic influenza, most notably in the infamous Spanish Influenza of 1918. In 1918, it was not known that the disease was caused by a virus, and part of the world was still embroiled in a devastating war. That virus, however, was not a coronavirus, and the diseases, the populations most affected, and healthcare systems were very different. It is, however, instructive to compare some of the historical events of the Spanish Influenza of 1918 to the COVID-19 pandemic of 2020, such as how different places dealt with the unmanageable surge in the number of cases.

The last chapter of this book is about testing, our immune system, and how our immune system recognizes the virus. I will also be talking about vaccines, how they work, how long they last, and how mutations can hinder the immune response, among other things. We have now witnessed the most rapid development and widespread deployment of vaccines in human history. Within a few months of the initial outbreak in Wuhan, several vaccines were being tested in humans, and a year later the population was being vaccinated at an unprecedented rate. This astonishing enterprise, together with the societal awareness of the dangers of emerging infectious diseases, left us wondering if we will be better prepared for potential future pandemics.