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

CHAPTER 14

Conclusions

INTRODUCTION

We live in an age of constant change, due, to a large degree, to the continuing threat of infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19. This recently emerged pandemic coronavirus has spread throughout the world. Countries or parts of countries have responded by locking down segments of their areas, in some cases, literally preventing the population from leaving their homes. Some other places were less stringent and only locked down places where people may gather and spread the virus. Often, this led to only "essential" services remaining open, while small and large businesses, places of worship, and fitness facilities were closed. Much of life is a trade-off: The closure of business most likely was an important factor in slowing the spread of the disease and "flattening the curve" so as to prevent hospitals from being overwhelmed. Unfortunately, the closures will most likely lead to the permanent loss of jobs and income. The effects of these lockdowns have also triggered crises in mental health, increasing depression, and, in some cases, suicide incidence. Many of our elderly population, especially those living with comorbidities, are very vulnerable to developing fatal disease if they were to become infected. However, these people have been isolated from their families and many will die without having the chance to physically be with their loved ones. Our physical health is also threatened, not only for those sickened or killed by SARS-CoV-19, but also for people with other, noncritical, medical conditions, who may not have access to hospitals or testing facilities.

Many methods have been employed to slow the spread of this virus. We have either mandated or strongly encouraged people to wear various types of facial coverings whose effectiveness is controversial among those in the scientific and medical community. We have practiced social distancing. In many areas, we have closed parks and other recreational venues, replaced face-to-face schooling with online classes, and closed places of worship. We did succeed in flattening the curve in many places for months, yet some parts of the developed world are now seeing the numbers of reported cases spiraling out of control as the number of new cases breaks records daily. Some of the increase in the number of people testing seropositive may be due to the massive testing efforts detecting more cases. Some of the increase may result from the reopening of businesses and other venues, which led to the exposure and spread of disease among those previously isolated from contact with infected people. Fortunately, the mortality rate is decreasing.

A second round of COVID-19-related shutdowns has been advocated in some areas, but as time goes by, thoughts about implementing this drastic action continue to change. The economic and societal impacts of both our inactions and actions will likely be felt for many years. If another round of shutdowns is mandated, this action may save lives or damage the world's economic health even further or both. Shutdowns are particularly devastating to impoverished people in the developed world and, even more so, to those living in the developing world. As the numbers of COVID-19 cases and hospitalizations continue to increase in some parts of the world, our understanding of the disease and our responses to it must also change. However, the resulting uncertainty in what constitutes the best practice for different segments of the population has caused rifts among scientists, physicians, and public health workers, in addition to the general population. The world post-COVID-19 may in some respects not ever return to the world that we knew before the emergence of SARS-CoV-2. Our previous jobs and understanding of a work environment, manner and quality of education, societal and cultural norms, and personal liberties may be irreversibly altered.

These major changes in our lives and our world occurred rapidly from the time that the first cases of COVID-19 were reported in China in December 2019 to the time of this writing (late July 2020). The emergence, spread, and increased virulence of other neglected viruses and viral diseases have also occurred in the previous two to three decades, most notably the rapid emergence of Zika virus-induced microcephaly among newborns and infants and Guillain–Barré syndrome in some Zika virus-infected adults. While the recent, large, and deadly Ebola outbreak did not seriously threaten the lives of people living outside of

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certain parts of Africa, it was devastating to the populations of the affected regions. Just as importantly, that Ebola outbreak occurred in an area of Africa that had previously been almost totally Ebola virus-free. Other large disease outbreaks in the previous decades include SARS, caused by a coronavirus that emerged in China and Hong Kong. It was quickly spread by air travel of infected people to other areas of the world and led to a major outbreak in Canada. The H5N1 avian influenza outbreak in 1997 was predicted to kill up to 100 million people, but instead killed less than 600 people over the course of two decades. The general public responded to the projected death rate with great fear that fortunately was unwarranted. Some leaders of the public health community are currently warning of a potential pandemic of a novel strain of H1N1 influenza during the next "flu" season, in addition to a second wave of COVID-19. Public health recommendations and mandates may again be implemented that threaten to rip apart the fabric of human society even further.

FLAVIVIRUSES AND THEIR VECTORS

This book dealt with the potential threats of novel or neglected flaviviruses or flaviviruses that have the potential to emerge or reemerge as they adapt to better survive and replicate in human hosts. Natural or man-made changes to the environment and ecosystems further disrupt long-standing viral transmission cycles as the behavior and range of the viruses' vector and reservoir species change. Since almost all flaviviruses are arboviruses, transmitted by mosquitoes and ticks, measures have been undertaken to decrease human exposure to the disease vectors, including extensive educational programs. The effectiveness of some of these measures is unknown. The vast campaign to contain West Nile virus in North America to New York City and the surrounding area appears to have been unsuccessful since the virus spread from coast to coast in the United States and southward and northward into Mexico and Canada in less than 5 years. We do not know, however, the extent to which this campaign mitigated the incidence of severe West Nile cases. Fortunately, while still a threat, the number of West Nile cases in much of North America peaked between 2003 and 2006. This is likely due to the decreased number of immunologically naïve human hosts resulting from herd immunity caused by large numbers of prior, asymptomatic cases.

Severe diseases caused by other flaviviruses, particularly dengue hemorrhagic fever and dengue shock syndrome, are continuing to spread as mosquitoes adapt to life in urban conditions (*Aedes aegypti*) and increase their range into more temperate zones (*Aedes albopictus*). Decreasing human exposure to mosquitoes and ticks should decrease disease incidence in humans. Large-scale, long-term elimination of these vector populations would, however, be extremely difficult. We have, however, had some significant successes in decreasing populations of disease-carrying mosquitoes. These successes include the dramatic reduction of yellow fever in Panama, which allowed the construction of the Panama Canal. Nevertheless, many areas that had substantially reduced mosquito populations are now seeing their return. Over a century ago, yellow fever was also virtually eliminated from the mainland of the United States, where it had previously occupied areas of the American South. These areas are still free of nontravel-related yellow fever.

FLAVIVIRUSES AND POTENTIAL ANIMAL RESERVOIR HOSTS

Flaviviruses in Bats

Bats have been suggested to be the original source of many viruses that are currently causing outbreaks in humans. Antibodies to several species of flaviviruses that are pathogenic to humans have been detected in bats, particularly in the Americas. A study conducted in Central and South America found that 20%–30% of the tested bats had neutralizing antibodies against dengue viruses 1–3 (DENV-1, DENV-2, and DENV-3).[1,2] All four DENV serotypes were present in Mexican bats. DENV has also been reported in Australian bats.[3]

In the northern United States, 1%–2% of big brown bats were seropositive for West Nile virus (WNV).[4] Several other North American bats are also seropositive for WNV. Antibodies to Saint Louis encephalitis (SLE) have also been found in about 9% of big and little brown bats.[5] SLE has also been isolated from Mexican free-tailed bats in Texas in the far south of the western United States. Neutralizing antibody was found in the sera of 20% of the tested bats.[6] In Trinidad, however, none of 14 tested species of bats ($n = 384$) were seropositive for WNV or SLE virus, another pathogenic flavivirus of humans found in North America.[7]

Flavivirus-seropositive bats have also been detected in Asia and Australia. Neutralizing antibodies against Japanese encephalitis virus (JEV) were found in the sera of 25% of the tested bats from southern China.[2,8] Viral RNA was not, however, detected in the brain of these animals. Five Australian flying foxes that were infected by exposure to JEV-infected *Culex annulirostris* mosquitoes remained asymptomatic and did not develop a detectable level of viremia.[9] Three species of Indian bats are also known to be seropositive for Kyasanur Forest disease virus.[2]

Flaviviruses and Rodents

In addition to bats, rodents have been implicated as major reservoir hosts for many microbes, including viruses. They have been, accordingly, the focus of a large amount of research in order to determine whether or not they are: (1) able to be infected with various types of viruses, (2) able to serve as competent hosts to pass the virus on to the virus' invertebrate vector, and (3) able to be used as sentinel animals to detect newly emerging human pathogens. Rodent species in most continents, to a greater or lesser degree, either have been reported to have flavivirus RNA in their tissues or are seropositive. Some of the tested rodents have close contact with humans in urban environments, while others have little contact with people. The former group is more likely to serve as important reservoirs of species of flavivirus that are or may become pathogenic to humans.

In North America, there is a paucity of pathogenic flaviviruses in rodent populations.

In Mexico, none of the rodent serum samples ($n = 708$) were positive for DENV-2, even though this virus is present in humans in the area.[10] While no Powassan flaviviruses have isolated from North American deer mice, they are seropositive for Powassan virus.[11]

In Europe, tickborne encephalitis virus (TBEV) was detected in six German rodent species: 13% of striped field mice, 8% of yellow-necked mice (8%), 29% of wood mice, 7% of field voles, 10% of common voles, and 13% of bank voles.[12] A study from Italy found that 4 of 90 yellow-necked mice from Italy were seropositive for WNV.[13] A study of 242 rodents and small mammals in Croatia, however, did not detect any flavivirus RNA.[14]

Several species of rodents are hosts to flaviviruses in Asia. In China, 46% of the tested brown and lesser ricefield rats ($n = 198$) were seropositive for anti-JEV IgG antibodies, but no viral RNA was found in the rodent brain samples.[15] In southern Vietnam, 5% of 275 tested rodents were seropositive for TBEV in an area in which 47% of 245 humans were positive.[16] TBEV RNA or E protein was present in 71% of the tested small mammals in Siberia, including northern red-backed voles, gray red-backed voles, northern bush mice, and striped field mice.[17]

In Africa, Usutu virus was isolated from two species of rodents in Senegal: the black rat and the multimammate mouse. Wesselsbron virus (WSLV) was isolated from a black rat in Senegal as well.[18,19]

Flaviviruses and Domestic Animals

In addition to adverse effects on humans throughout the world, some flaviviruses cause severe, life-threatening disease in animals, including birds, horses, and sheep. Some flaviviruses cause abortions in domestic animals, such as sheep and cattle. Other flaviviruses, however, use domestic animals as reservoirs or amplifying hosts. A meta-analysis found that only 4% of the tested bats were competent hosts for JEV, as opposed to 50% or more of the tested cattle, pigs, horses, donkeys, cats, and dogs.[20,21]

Due to our close interactions with our domestic animals, they may play a far greater role in zoonotic transmission of pathogenic flaviviruses than we realize. Agricultural animals, particularly cattle, as well as our companion animals, are known to be infected with several different flaviviruses. A study performed in Hungary found 27% of the tested cattle and 7% of the sheep, but no horses, were seropositive for TBEV.[22] TBEV is also excreted in the unpasteurized milk of goats, sheep, and cattle and is active for several days, even if refrigerated.[23] TBEV-FE has been isolated from dogs in Japan as well.[24] A high percentage of Australian cattle are seropositive for Murray Valley encephalitis virus.[25] Furthermore, serological evidence supports the presence of JEV antibody in 78% of the tested dogs, 52% of the cattle, 34% of the pigs, and 21% of the goats.[26] In a Malaysian survey, 80% of the dogs were seropositive for JEV, as well as 44% of the pigs, 32% of the cattle, and 16% of the cats.[27] In addition to causing disease in sheep and cattle, WSLV has been isolated from pigs, donkeys, camels, and horses in Africa.[28] A study of hunting dogs in southern Italy found serological evidence of Usutu virus in 13% of the tested animals as well.[29]

While some species of bats and rodents are infected with several flaviviruses that are pathogenic to humans, the number of flavivirus species and the incidence of infection in cattle and sheep are much greater than those found in bats or rodents. In light of the above information, perhaps more time and resources should be directed toward studying the risk of potentially pathogenic viruses using domestic animals as reservoir hosts.

PREPARATIONS FOR THE FUTURE

Once humans began to live in population centers that were large enough to allow sustained transmission of microbes from infected to immunologically naïve people, our species have been repeatedly hit by rounds of infectious disease outbreaks. Even the relatively slow methods of travel allowed the spread of infection to distant areas. However, with the discovery of compounds such as sulfa drugs and antibiotics and their increasing availability to the general population, humans began to curb the number of infections and deaths from infectious diseases in most of the developed world. Childhood diseases were disappearing due to the development of effective vaccines. During the late 1970s, a victory over infectious diseases, particularly

over bacterial and parasitic illnesses, was proclaimed by many in the medical field as we began to increase our focus on preventing and treating other diseases, including those affecting the cardiovascular and respiratory systems, cancers, diabetes, and obesity.

Unfortunately, our proclamation of victory was premature as bacteria, including staphylococci and the *Mycobacterium* species responsible for tuberculosis, and parasites, such as the causative agents of malaria, became drug-resistant. Viruses, such as HIV, and influenza and Ebola viruses, are also not susceptible to antibiotics. The rapid rate of mutation of RNA viruses complicates the development of effective vaccines and drugs, making it very difficult to adequately prepare for large outbreaks of new strains of viruses as well as the emergence or reemergence of other viruses. The politicians and general population often fail to grasp the difficulty in the fight against viral infection. Many of the methods that had worked so successfully against bacterial infections for decades do not always work against viral infections. Other types of responses need to be developed to detect and mitigate outbreaks of viral diseases. This is especially important due to the rising number of our elderly population as well as the increased number of immunocompromised people, including those being treated for autoimmune conditions or cancer, those with respiratory or cardiovascular conditions, diabetics, and the obese.

To prepare more adequately for the next viral pandemic(s), we need to develop more broad-spectrum antiviral drugs in the same manner as we had previously developed different types of antibiotics. The process of producing antiviral compounds and vaccines will be much more difficult, however, given the rapid rate of mutation of some viruses and the tendency of antiviral drugs to produce serious side effects. We need to continue to repurpose older drugs as well. We also need to detect the emergence of new viral threats or the reemergence of older viruses to give ourselves the time in which to respond and curtail the spread of these diseases. Monitoring the potential for zoonotic transmission of newly emerging viruses or the spread or increased pathogenicity of neglected viruses could buy us this valuable time. While future viral pandemics are inevitable, we may then be better prepared to stop their spread and to treat them.

CANDIDATES FOR THE NEXT PANDEMIC?

Other mosquito-borne flaviviruses are also able to at least occasionally infect humans asymptomatically or may produce febrile disease that is usually self-resolving. The following flaviviruses are present in Australia or New Guinea: New Mapoon, Torres, Fitzroy, Edge Hill, Sepik, and Alfuy viruses. Infection with Edge Hill, Sepik, and Alfuy viruses may result in a mild, febrile illness. The following flaviviruses are from Africa: Bainyik, Koutango, Uganda S (including Banzi), Ntaya, and Spondweni viruses. Of these, Uganda S, Ntaya, and Spondweni viruses may cause a febrile illness. Ntaya virus may also cause headache, myalgia, and rigors. Spondweni virus is closely related to Zika virus, and infection may asymptomatic; mild and febrile; or cause headache, nausea, muscle and joint pain, conjunctivitis, and rash. It is also found in some Caribbean islands, including Puerto Rico and Haiti. In Asia, other neglected mosquito-borne flaviviruses include ThCAr virus.

Other tickborne flaviviruses may cause mild to severe illness as well. These include the nonpathogenic Gadgets Gulley virus from Australia and Kadam virus from Africa and the Middle East. Royal Farm (Karshi) virus from Afghanistan may cause a febrile illness, and Langat virus from Asia may cause Siberian fever and encephalitis. Two newly discovered members of the Flaviviridae family from China, the Alongshan and Jingmen tick viruses, while not from the flavivirus genus, cause mild, febrile disease in China.[30,31]

The above listed viruses are only some of the flaviviruses that may pose serious threats to humans if they increase their pathogenicity. Flaviviruses from other animals, especially our agricultural animals, also may at some point gain the ability to transition into new hosts, including humans. We need to remain vigilant in our monitoring of these and other microbes, but not panic. We need to carefully balance our safety and responsibility to our most vulnerable people against our economic and mental health needs as well as our personal liberties and the overall health of human societies. It is a difficult balancing act, but one that we have faced in the past and will continue to do in the future.

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