Chapter 1

SARS-CoV-2 and COVID-19: A Perspective

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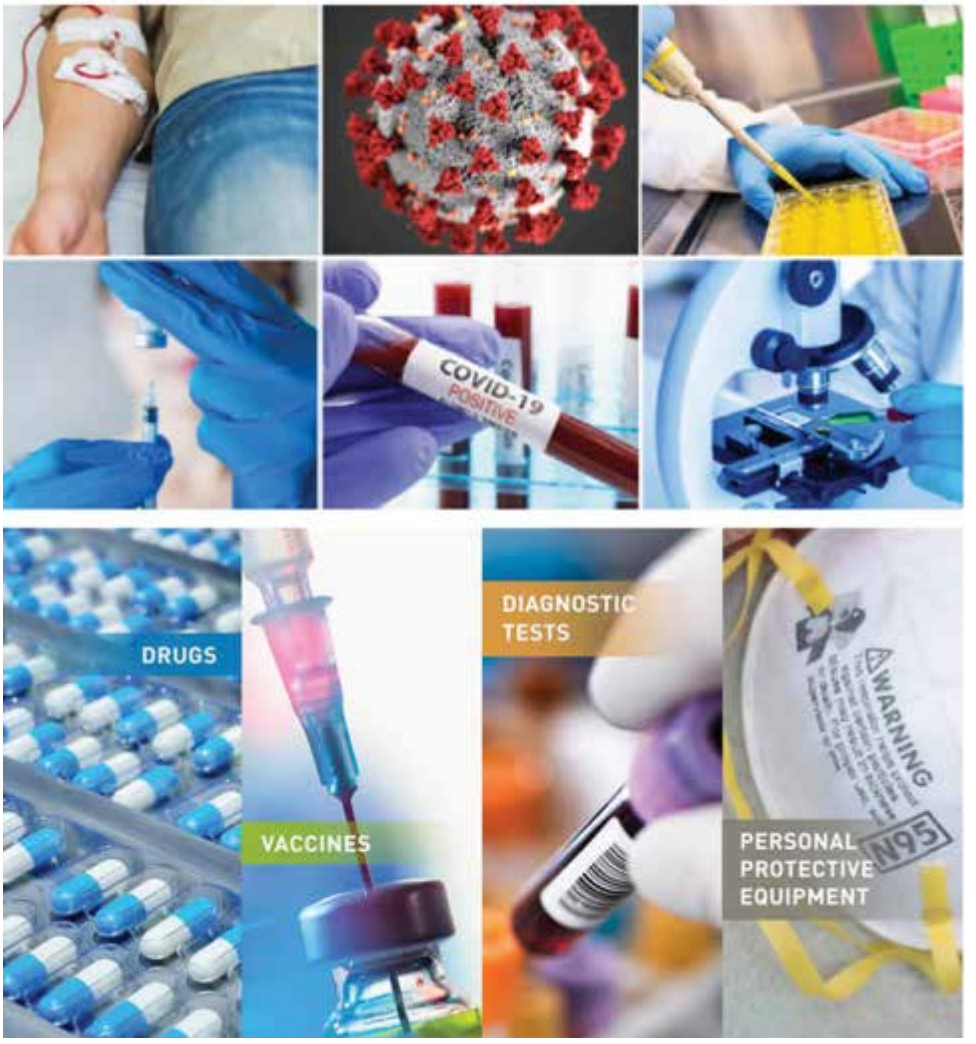

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I dedicate this chapter to my late mother, Mrs. Sudesh Bawa (1935–2020), in whose memory I have established the *Sudesh Bawa Medical Foundation*. This section is based, in part, on discussions I have had with my 92-year-old father, Dr. S. R. Bawa, an anatomist and a retired university professor/chair. My parents were married in 1954 and exemplified how a lifelong relationship of love, dedication and perseverance gives meaning to life.

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1.1 Pandemics: A Clear and Present Danger

Messieurs, c'est les microbes qui auront le dernier mot.
(Gentlemen, it is the microbes who will have the last word.)

—Louis Pasteur

Epidemics on the other side of the world are a threat to us all. No epidemic is just local.

—Peter Piot

As a microbiologist, I am fully aware that our world is a playground for microbes. Emerging pathogens pose a clear and present danger, and pandemic preparedness is critical. Pandemics can be triggered by unavoidable or uncontrollable natural processes like genetic variations and climate change. They can also arise from risks generated by human activities or practices. Examples include antibiotic

overuse or misuse, destruction of forest habitats of microbe-carrying animals, and an increase in the ease and speed of global transportation that spreads disease-causing pathogens. By some estimates, of the 1,461 diseases now recognized in humans, approximately 60% are due to multi-host pathogens characterized by their movement across species lines.[1] Other reports conclude that over the past three decades about 75% of new emerging human infectious diseases have a zoonotic origin.[2] Clearly, human-animal interactions and interdependence are likely the most critical risk factor to our health regarding infectious diseases. To gauge a "spillover event" enormous scientific resources are directed towards predicting where the deadliest viruses reside, their life cycles, susceptibilities, and ability to cross species barriers.

Throughout history, viruses, bacteria, and parasites have killed more humans than wars and natural disasters. Viral diseases were recorded ever since humans began living together in communities, with smallpox being the first reported around 10,000 BC. Smallpox was the deadliest human disease to ever exist with a devastating 20–60% mortality rate, killing an estimated 300 million people in the 20th century alone. In 1918, the H1N1 Spanish Flu infected one-third of the world's population and killed an estimated 50–100 million people. Other recent influenza pandemics include the 1957 H2N2 (Asian Flu) that originated in China and killed around 4 million people worldwide, the 1968 H3N2 (Hong Kong Flu) that killed 1 million people worldwide, the 2005 H5N1 (Bird Flu) which caused few deaths and the 2009 H1N1 (Swine Flu) which caused 18,000 human deaths.

In addition to influenza pandemics, coronaviruses have also caused regional epidemics prior to the current COVID-19 pandemic (Figs. 1.1–1.4). Coronaviruses of zoonotic origin have caused large-scale cluster outbreaks of severe respiratory disease. These include the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) epidemic in 2003 in mainland China and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) epidemic in 2012 in Saudi Arabia and in 2015 in South Korea. SARS-CoV (the first coronavirus) spread to 26 countries before the outbreak was contained with over 8,000 people infected and a case fatality rate of approximately 10%. Regarding MERS-CoV, infections are still occurring and have been reported in almost 30 countries. While human-to-human transmission for MERS-CoV is rare, some studies show the case fatality rate to be greater than 30%.

The year 2020 will forever be marked by the presence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[3] and the associated COVID-19 pandemic. COVID-19 has had a catastrophic effect on the world's

[1]E. F. Torrey and R. H. Yolken. (2005). *Beasts of the Earth*. Rutgers University Press, New Brunswick, NJ.

[2]L. H. Taylor, S. M. Latham, and M. E. Woolhouse (2001). Risk factors for human disease emergence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**:983–989.

[3]It is important to distinguish the SARS-CoV-2 virus from the disease it causes, namely, COVID-19. In this chapter, I will use the terms SARS-CoV-2 virus, CoV-2 virus, and coronavirus 2 interchangeably to refer to the virus that causes COVID-19.

demographics resulting in ~3.76 million deaths so far. After the first cases of this predominantly respiratory viral illness were "officially" reported by the Chinese government in late December 2019, SARS-CoV-2 rapidly circumvented the globe in a matter of weeks, compelling the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020. As of June 8, 2021, globally, there have been 174,591,505 coronavirus cases and 3,757,419 deaths, and 157,941,391 patients have recovered from COVID-19.[4] Virtually overnight, this pandemic profoundly altered the world as it struggled to contain the coronavirus while mitigating its health, economic and social impact. *For a global pandemic to occur, the following requirements are needed: emergence of a new human microbe; reduced or minimal population immunity to that microbe; and a relatively simple mode of transmission. SARS-CoV-2 fulfills all three of these criteria.*

1.2 The Invader and the Host: A Delicate Dance

The viruses, instead of being single-minded agents of disease and death, now begin to look more like mobile genes. We live in a dancing matrix of viruses; they dart, rather like bees, from organism to organism, from plant to insect to mammal to me and back again, and into the sea, tugging along pieces of this genome, strings of genes from that, transplanting grafts of DNA, passing around heredity as though at a great party. They may be a mechanism for keeping new, mutant kinds of DNA in the widest circulation among us. If this is true, the odd virus disease, on which we must focus so much of our attention in medicine, may be looked on as an accident, something dropped.

—Lewis Thomas, *Lives of a Cell: Notes of a Biology Watcher*, 1974

A delicate dance between a virus (the invading pathogen) (Figs. 1.1 and 1.2) and the immune system (host defense mechanisms) unfolds each time the virus infects the host (Figs. 1.3 and 1.4). Host immune cells and antibodies are in constant battle with virus invaders, with one just barely keeping the other in check. One of the most confusing and fundamental questions around viruses is why they are severely pathogenic to some hosts and asymptomatic in others. After all, it is in the virus's best interest, from an evolutionary perspective, to co-exist in the host in a chronic asymptomatic state without causing major damage. Smart viruses maintain a carrier state, a sort of equilibrium with the host's immune cells in an asymptomatic fashion.

[4]Worldometer. COVID-19 outbreak live update. Available at: https://www.worldometers.info/coronavirus (accessed on June 8, 2021). Another authoritative source is the Johns Hopkins Coronavirus Resource Center: https://coronavirus.jhu.edu/. Please note that limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the actual number of deaths from COVID-19.

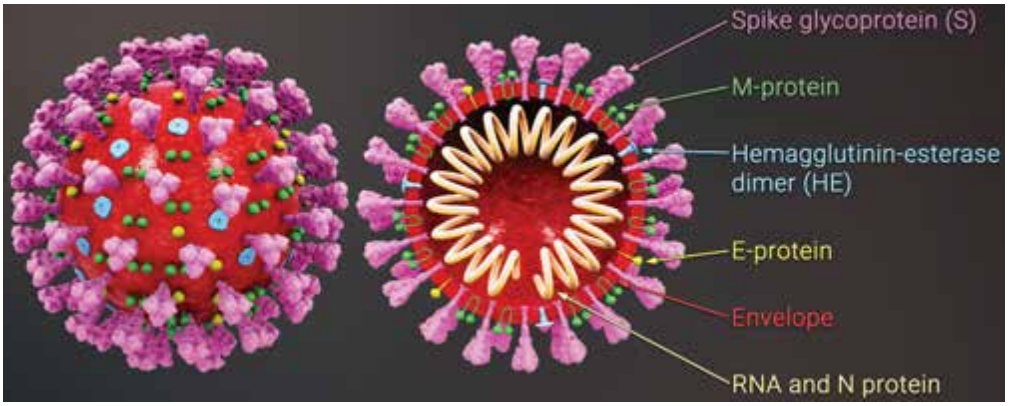

Figure 1.1a Structural view of a coronavirus. *Source*: https://commons.wikimedia.org/wiki/File:3D_medical_animation_coronavirus_structure.jpg.

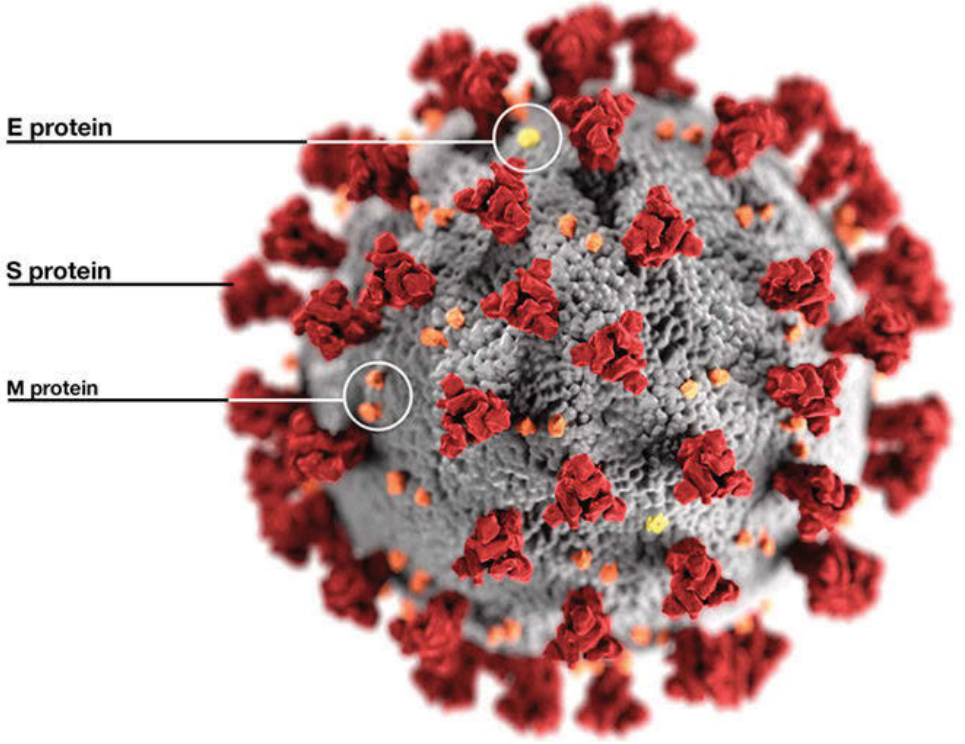

Figure 1.1b The peplomers of a SARS-CoV-2. This illustration reveals the surface morphology/topography of the virus nanoparticle. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding it, when viewed electron microscopically. A peplomer (Greek: *peplos*, 'robe', '[woman's] dress' + *meros*, 'part') is one of the knoblike spike structures (red, orange), generally composed of glycoproteins (spike protein) and projecting from the lipid bilayer of the surface envelope. Peplomers play important roles in the infection process. *Figure courtesy of the CDC*.

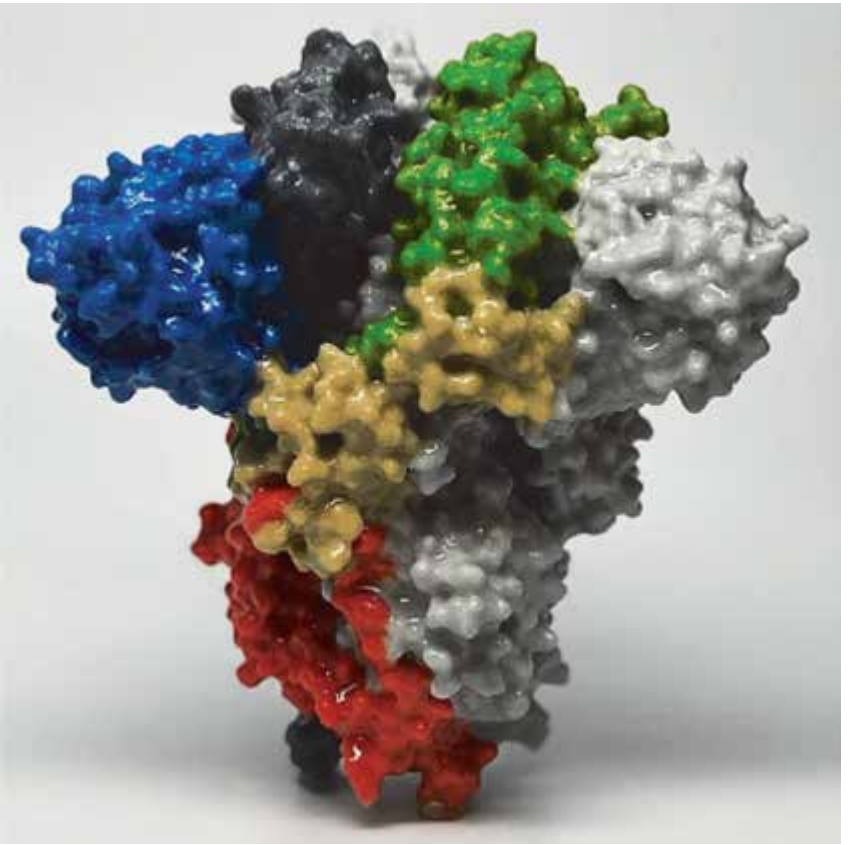

Figure 1.1c 3D print of one of the peplomers of SARS-CoV-2. *Courtesy of NIH.*

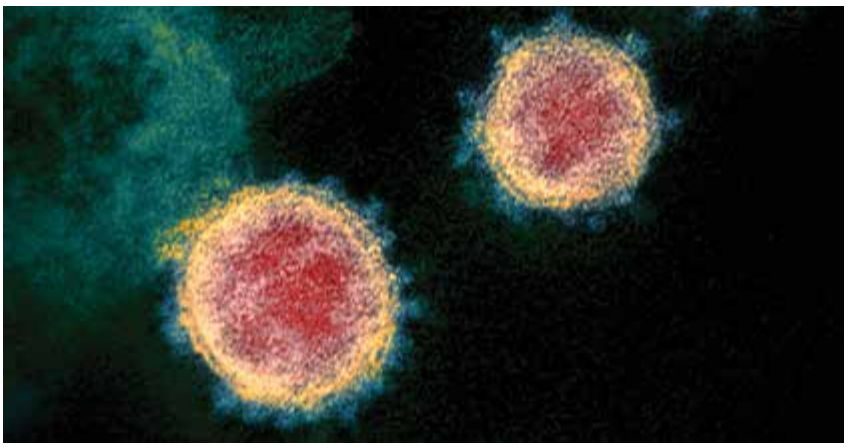

Figure 1.2 Digitally colorized transmission electron micrograph of SARS-CoV-2. Virus particles isolated from a patient in the US are shown emerging from the surface of cells cultured in the lab. *Courtesy of NIH.*

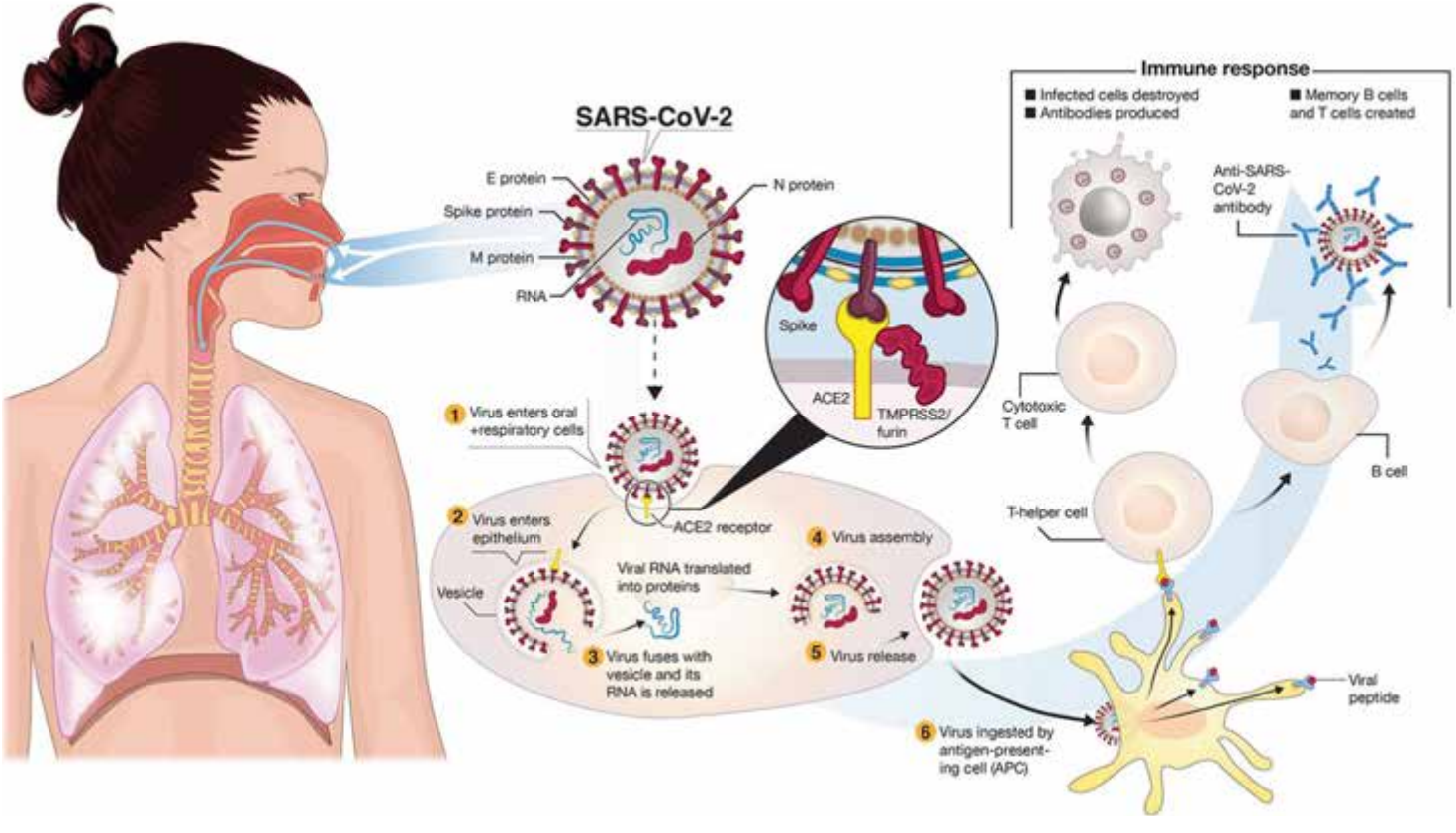

Figure 1.3 Transmission and life cycle of SARS-CoV-2 causing COVID-19. SARS-CoV-2 is transmitted via respiratory droplets of infected cases to oral and respiratory mucosal cells. The virus, possessing a single-stranded RNA genome wrapped in nucleocapsid (N) protein and three major surface proteins: membrane (M), envelope (E), and spike, replicates and passes to the lower airways potentially leading to severe pneumonia. The gateway to host cell entry (magnified view) is via Spike-converting enzyme 2 (ACE2) interaction with cleavage of spike in the prefusion state by proteases TMPRSS-2/furin. A simplified depiction of the life cycle of the virus is shown along with potential immune responses elicited. *Source*: C. D. Funk, C. et al. (2020). A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. *Front. Pharmacol.* **11**:937.

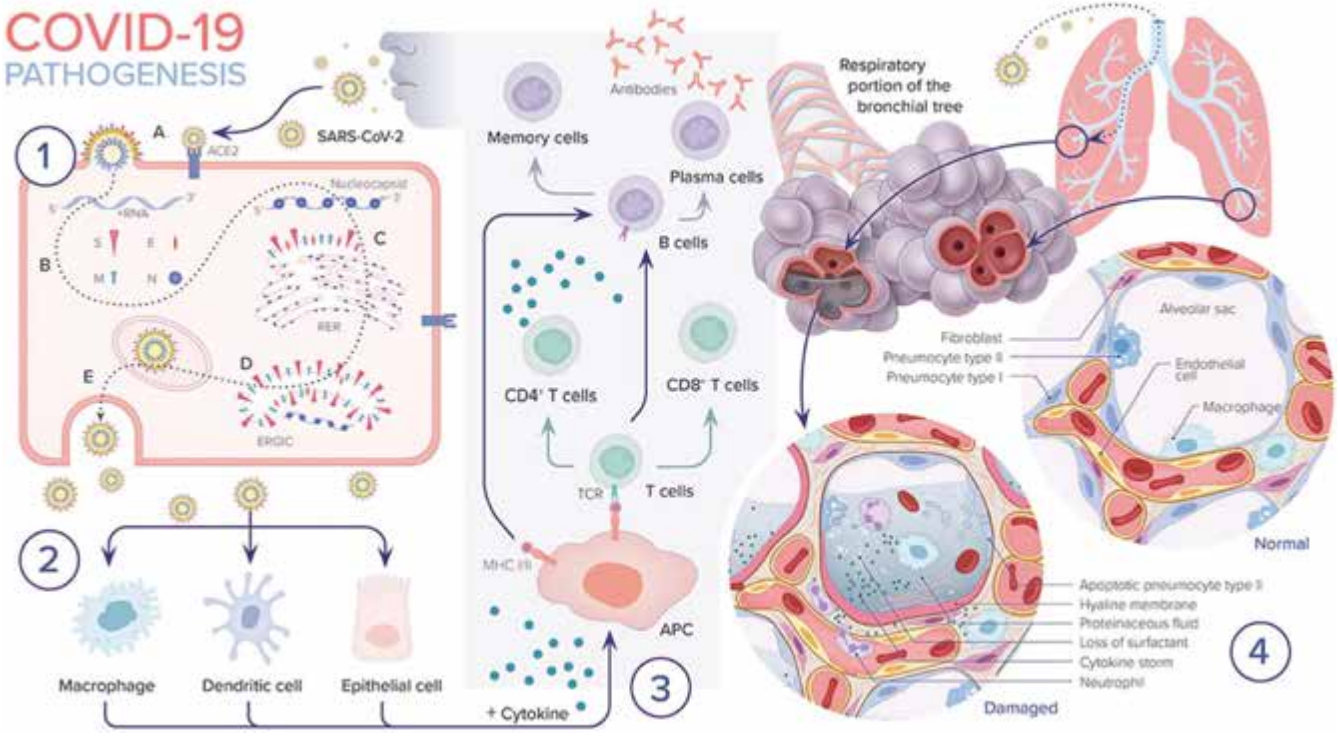

Figure 1.4 COVID-19 pathogenesis. 1. A. SARS-CoV-2 enters the epithelial cell either via endocytosis or by membrane fusion through binding to ACE2 receptor and releasingits RNA into the cytoplasm. B. Viral RNA uses the cell's machinery to translate its viral non-structural and structural proteins and replicate its RNA. C. Viral structural proteins S, E, and M assemble in the rough endoplasmic reticulum (RER). D. Viral structures and nucleocapsid subsequently assemble in the endoplasmic reticulum Golgi intermediate (ERGIC). E. New virion packed in Golgi vesicles fuse with the plasma membrane and gets released via exocytosis. 2. SARS-CoV-2 infection induces inflammatory factors that lead to activation of macrophages and dendritic cells. 3. Antigen presentation of SARS-CoV-2 via major histocompatibility complexes I and II (MHC I and II) stimulates humoral and cellular immunity resulting in cytokine and antibody production. 4. In severe COVID-19 cases, the virus reaches the lower respiratory tract and infects type II pneumocytes leading to apoptosis and loss of surfactant. The influx of macrophages and neutrophils induces a cytokine storm. Leaky capillaries lead to alveolar edema. Hyaline membrane is formed. All of these pathological changes result in alveolar damage and collapse, impairing gas exchange. *Source*: N. Chams, et al. (2020). COVID-19: a multidisciplinary review. *Front. Public Health* **8**:383.

1.3 Did SARS-CoV-2 Leak from a Chinese Lab?

Life on Earth is at the ever-increasing risk of being wiped out by a disaster, such as sudden global nuclear war, a genetically engineered virus or other dangers we have not yet thought of.

—Stephen Hawking

Is it possible that SARS-CoV-2 began when an animal virus found its way unaided into humans, i.e., a zoonotic spillover? Is it more likely that the virus began in a Chinese government laboratory in Wuhan? Was it genetically engineered at the lab to enhance its virulence and infectivity? Is it a man-made bioweapon? Was SARS-CoV engineered into SARS-CoV-2? Did it accidentally leak from the lab? We do not know the precise answer to these critical questions at the moment. But, strong circumstantial evidence is building that points towards a lab leak and Chinese cover-up.

China's response to the COVID-19 outbreak has been scrutinized since the virus was first detected in its Wuhan province. In fact, China's lack of transparency and questionable tactics, especially in the first few weeks, have contributed to the spread of SARS-CoV-2. This has led to calls for an open investigation into the possibility that the coronavirus leaked from a lab. Even if SARS-CoV-2 originated naturally, from animal-human contact, it does not preclude the possibility that the virus was the result of an accidental leak from China's Wuhan Institute of Virology, where coronavirus research was being conducted on bats. This institute is only a few kilometers from the Huanan Seafood Market where SARS-CoV-2 was first detected.[5] To deflect blame for a potential leak, the Chinese government has promoted unsubstantiated theories that the virus may have entered China via frozen food.

The WHO does not have the regulatory authority to force governments to disclose information. It has been particularly weak dealing with China on the COVID-19 pandemic. China did recently invite a small WHO team of disease experts to "investigate" the outbreak, but its findings were of limited value since the team's constraints reveal how little power it had to conduct a fair probe. To me, this visit was akin to a student field trip where the final conclusions were predetermined and scientifically fraudulent. No wonder, the WHO was broadly criticized by many governments over its limited access to "complete, original data and samples" and overly deferential treatment of China throughout the course of this study. Moreover, this study was co-authored by 17 Chinese scientists, several of them from Chinese government-run institutions. As an editor of peer-reviewed journals for almost two decades, this represents a clear conflict of interest and scientific misconduct on the part of the authors of this "invalid" WHO report.

A US State Department fact sheet from January 2021 highlights reports of sick lab researchers at the Wuhan Institute of Virology in the fall of 2019. It also points

[5]On December 30, 2019, the Wuhan Municipal Health Commission issued two urgent notices to local hospitals about cases of pneumonia of unknown origin linked to the Huanan Seafood Market. The Wuhan Institute of Virology sequenced almost the entire genome of the virus on January 2, 2020. This sequence and further sequences were made public later in January 2020. Chinese scientists successfully isolated the virus by January 7, 2020, and developed a PCR testing reagent for the virus by January 10, 2020.

to research with virulent coronavirus strains and indicates secret Chinese military activity at the lab. In May 2021, strong evidence from a previously undisclosed US intelligence report was made available that details three researchers from this institute becoming ill enough to seek hospital care in the autumn of 2019.[6] Their illness occurred a few months prior to the official Chinese government disclosure of SARS-CoV-2 to the world. Clearly, more rigorous investigations are required to establish the original source of this pandemic, with or without China's assistance. I predict that the Chinese government will continue to stonewall any efforts to determine the true origins of SARS-CoV-2. As a side note, the question has also arisen if plaintiffs from other countries can sue China for COVID-19 and hold it legally accountable in their respective courts. In fact, first lawsuits against the government of China and the Chinese Communist Party were filed in 2020 with a heavy emphasis on mass torts and class actions.[7] However, a major obstacle to these lawsuits is the bedrock doctrine of sovereign immunity which protects a nation from being sued in another nation.

As an adjunct professor at Rensselaer Polytechnic Institute in Troy, NY, from 1998 to 2018, I designed and taught a course for over a decade titled "Biodefense: A clear and present danger." It included lectures on emerging and re-emerging infectious diseases and noted the potential of coronaviruses to cause pandemics. A few lectures covered microbial bioweapons and biodefenses against them. The inspiration for the course was based on a half-day meeting at the Center for Biodefense at George Mason University in Virginia with its director, Dr. Kenneth "Ken" Alibek (Col. Kanatzhan "Kanat" Alibekov). He was the First Deputy Director of Biopreparat from 1988–1992, the offensive biological weapons program of the Soviet Union. This gigantic clandestine biowarfare project, at its height, had 50,000+ employees. There, he oversaw projects that included weaponizing microbes that cause glanders, smallpox, plague, tularemia, Ebola, and Marburg, and the creation of a new "battle strain" of anthrax. The size and scope of the Soviet Union's bioweapon's efforts were truly staggering. They stockpiled tons of anthrax bacilli and smallpox virus, some for use in intercontinental ballistic missiles. Dr. Alibek gifted me his superb book, titled *Biohazard*,[8] excerpts of which I have continued to use in the classroom for the past 15 years. The subtitle for the book, "The chilling true story of the largest covert biological weapons program in the world—Told from the inside by the man who ran it," is an appropriate summary of the book's contents. It is a must-read for any medical student, microbiologist, policy-maker, or health-care professional. *The book highlights that (i) despite international conventions banning bioweapons development, secrecy regarding genetic manipulation of microbes to enhance their pathogenicity and virulence is a reality at state-run labs of numerous countries; and*

[6]M. R. Gordon, W. P. Strobel, and D. Hinshaw (2021). Intelligence on sick staff at Wuhan lab fuels debate on Covid-19 origin. *Wall Street J.*, May 23 issue. Among the first 27 documented hospitalized patients, most cases were epidemiologically linked to Huanan Seafood Wholesale Market, a wet market that sold live animals, including wildlife. On December 31, 2019, the Wuhan Municipal Health Commission notified the public of a pneumonia outbreak of unidentified cause and also informed the WHO.

[7]D. Ricker. (2020). Suing China for COVID-19. *ABA J.,* August/September issue, page 17.

[8]K. Alibek and S. Handelman. (1999). *Biohazard.* Random House, New York, NY.

(ii) the potential that the world's most dangerous pathogens can escape from biosafety labs, including the controversial biosafety level-4 (BSL-4) labs, is typically maintained as a state secret. Given this backdrop, it is possible that the Wuhan Institute of Virology created the SARS-CoV-2 virus via genetic engineering and it accidently leaked out into the nearby wet market, resulting in the current COVID-19 pandemic. If this did happen, it also points to the wider concern many experts have had that microbial leaks, even at BSL-4 labs like the one in Wuhan, present serious public health concerns. In fact, concerns were raised during the certification of the Wuhan Institute of Virology as meeting the standards of BSL-4 back in 2017: "Some scientists outside China worry about pathogens escaping, and the addition of a biological dimension to geopolitical tensions between China and other nations ... The SARS virus has escaped from high-level containment facilities in Beijing multiple times."[9] Such worries are real with documented leaks provided as evidence. Elaborate coverups, which possibly are also underway at Wuhan, are typical of dictatorships like China and Russia.[10] Tighter security is needed at BSL-4 labs to prevent theft, accidents, or terrorism.

1.4 COVID-19 Vaccines: Facts and Fiction

I hope that someday the practice of producing cowpox in human beings will spread over the world—when that day comes, there will be no more smallpox.

—Edward Jenner

Without equity, pandemic battles will fail. Viruses will simply recirculate, and perhaps undergo mutations or changes that render vaccines useless, passing through the unprotected populations of the planet.

—Laurie Garrett

Vaccines and immunizations are among the most effective public health interventions of the last century. They represent great strides in taming or conquering microbial diseases. By some estimates, 2.5 million child deaths around the world are prevented each year by immunization. According to recent Centers for Disease Control and Prevention (CDC) data, routine childhood vaccinations prevented 732,000 early deaths from 1994 to 2013.

1.4.1 The First COVID-19 Vaccines

Thankfully, there was positive news in early 2021 in the battle against SARS-CoV-2, though the war is far from won. Here in the US, the massive $10 billion investment of the Trump administration in Operation Warp Speed to fast-track

[9] D. Cyranoski. (2017). Inside China's pathogen lab. *Nature* **554**:339–340.

[10] See, F. Frischknecht. (2003). The history of biological warfare. *EMBO Reports* **4**:S47–S52: "In 1979, the Soviet secret police orchestrated a large cover-up to explain an outbreak of anthrax in Sverdlovsk, now Ekaterinburg, Russia, with poisoned meat from anthrax-contaminated animals sold on the black market. It was eventually revealed to have been due to an accident in a bioweapons factory, where a clogged air filter was removed but not replaced between shifts."

the development of SARS-CoV-2 vaccines within one year has paid dividends and resulted in a dozen or more potential vaccine candidates. Importantly, a few vaccines have been approved under an emergency use authorization (EUA)[11] and made available in the US, *albeit* the rollout has been disastrous. Currently, there are six approved vaccines authorized for use in select countries (Fig. 1.5a–c and Table 1.1): mRNA-1273 (Moderna/NIAID), BNT162b2 (Pfizer-BioNTech), Ad26.COV2.S (Johnson & Johnson/Janssen), ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), Gam-COVID-Vac/Sputnik V (Gamaleya Research Institute of Epidemiology and Microbiology, Russia), and BBIBP-CorV (Sinopharm/Beijing Institute of Biological Products, China). Based on published clinical trial data,[12] their efficacies range from 65.5% to 94.6% in preventing symptomatic COVID-19. The overall efficacies of the three FDA-authorized vaccines currently marketed in the US[13] (e.g., Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen)[14] tested prior to the emergence of deadlier variant varieties are in the 90%+ range. I am not sure how effective any of these first generation vaccines will be once they encounter multiple virulent variants of SARS-CoV-2.

Preliminary data reported in May 2021 from a trial of more than 600 people are the first to show the benefits of combining different vaccines (heterologous prime-boost). Such mix-and-match COVID-19 vaccination strategies may trigger stronger, more robust immune responses than will two doses of a single vaccine while simplifying immunization efforts where vaccine supplies are less reliable. I wonder what the long-term safety data of such an approach will be given that RNA vaccines (in contrast to traditional vaccines) tend to trigger stronger side effects with added doses?

It is important to note that for other coronaviruses, such as the common cold virus (SARS-CoV) and the MERS virus, immunity declines over time. But, at this stage, it is uncertain as to how long antibodies and immunity lasts for those

[11]In certain emergencies, the FDA can issue an EUA to provide more timely access to critical medical products (including medicines and tests) when there are no adequate, approved, and available alternative options.

[12]There were 549 clinical trials on COVID-19 recorded in early April 2020. By January 2021, there were already 4,000 studies registered. Available at: https://www.globaldata.com/covid-19-clinical-trials-increased-639-us-leading-way/ (accessed on June 8, 2021).

[13]Traditional vaccines contain ingredients to generate an immune response, usually protein fragments (active agents) of the microbe that causes the disease along with preservations and excipients (inactive agents). In the case of the COVID-19 vaccine, instead of using the whole virus to generate an immune response, vaccines formulations comprise RNA sequences correspond to the coronavirus' outer spike proteins, which are what antibodies use to recognize the virus. In other words, the genetic code used by the virus to synthesize the spike proteins is the active agent in the vaccine formulation. The RNA is protected by a lipid coating, forming a nanoparticle (technically it is a nanomedicine). When injected into a patient, the RNA enters healthy cells where it helps orchestrate the production of coronavirus spike proteins, kickstarting the immune system and producing antibodies.

[14]Two vaccines not (yet) available in the US are Oxford-AstraZeneca and Novavax. For an excellent comparison of all vaccines, see: Comparing the COVID-19 vaccines: How are they different? Available at: https://www.yalemedicine.org/news/covid-19-vaccine-comparison (accessed on June 8, 2021). Also see: COVID-19 vaccine & therapeutics tracker. Available at: https://biorender.com/covid-vaccine-tracker (accessed on June 8, 2021).

vaccinated, or even those exposed to the virus. In my assessment, we will require regular booster shots for the virus as novel variants continue to emerge and as COVID-19 morphs into a chronic multisystemic viral disease. More effective vaccines of broader scope, preferably single-shot, are urgently needed.[15]

As countries roll out vaccines against the SARS-CoV-2 virus, studies are under way to determine whether shots can also stop viral transmission as this could be critical to bringing the pandemic under control but only if enough people are vaccinated. Some studies suggest that some vaccines are likely to have a transmission-blocking effect. However, this is not easy to establish because a drop in infections can be due to other factors, such as lockdowns and personal behavior.

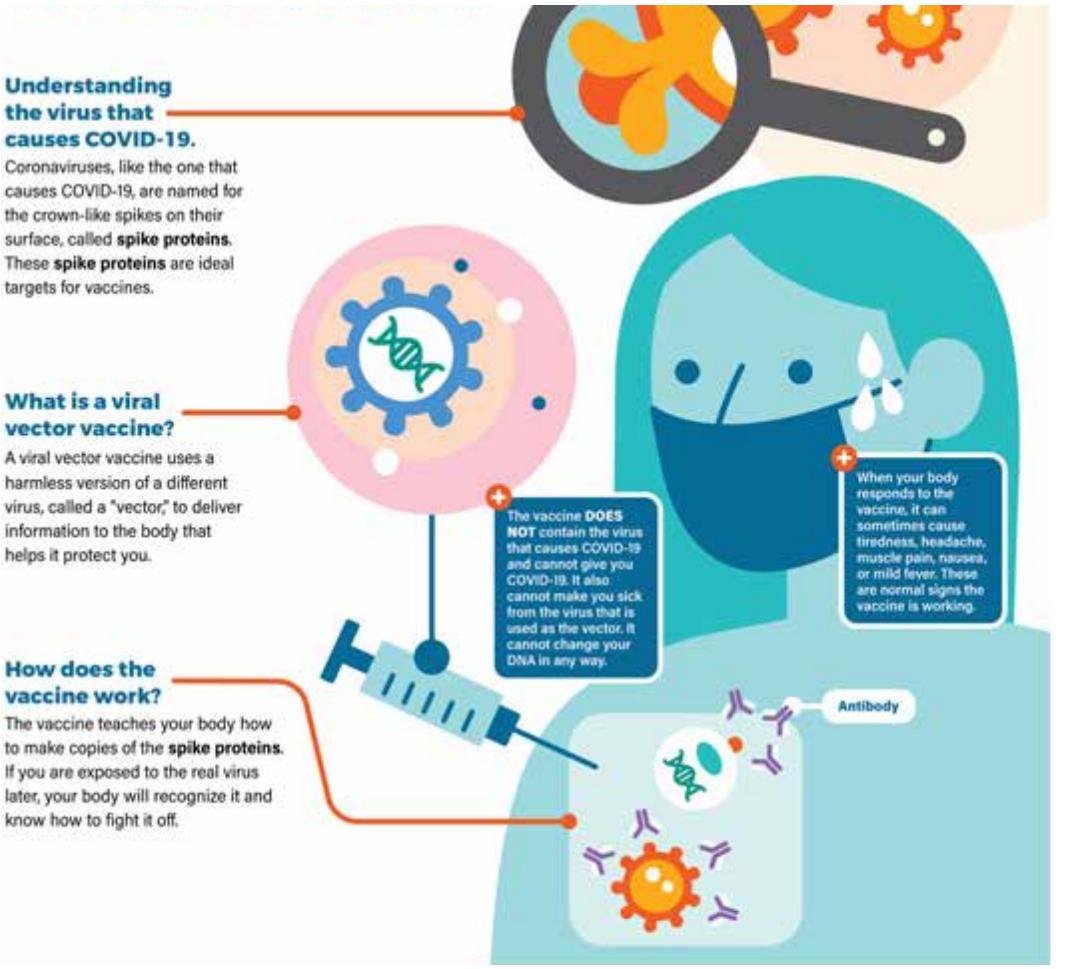

Figure 1.5a How viral vector COVID-19 vaccines work. *Courtesy of the CDC*.

[15]In May 2021, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) announced that it had approved a single-shot coronavirus vaccine developed by Johnson & Johnson/Janssen. However, it is 67% effective overall at preventing moderate to severe COVID-19, with studies suggesting that it also offers complete protection from admission to hospital and death. According to Johnson & Johnson, the vaccine works across multiple variants of coronavirus.

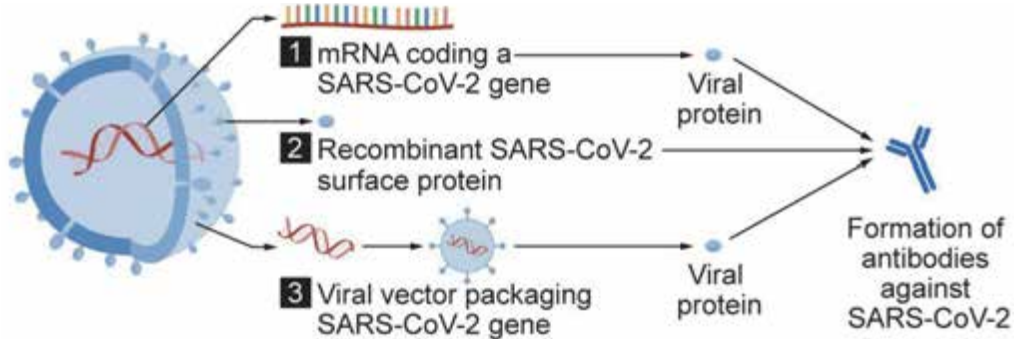

Figure 1.5b Three vaccine types for forming SARS-CoV-2 proteins to prompt an immune response: (1) RNA vaccine, (2) subunit vaccine, (3) viral vector vaccine. *Courtesy of the Government Accountability Office.*

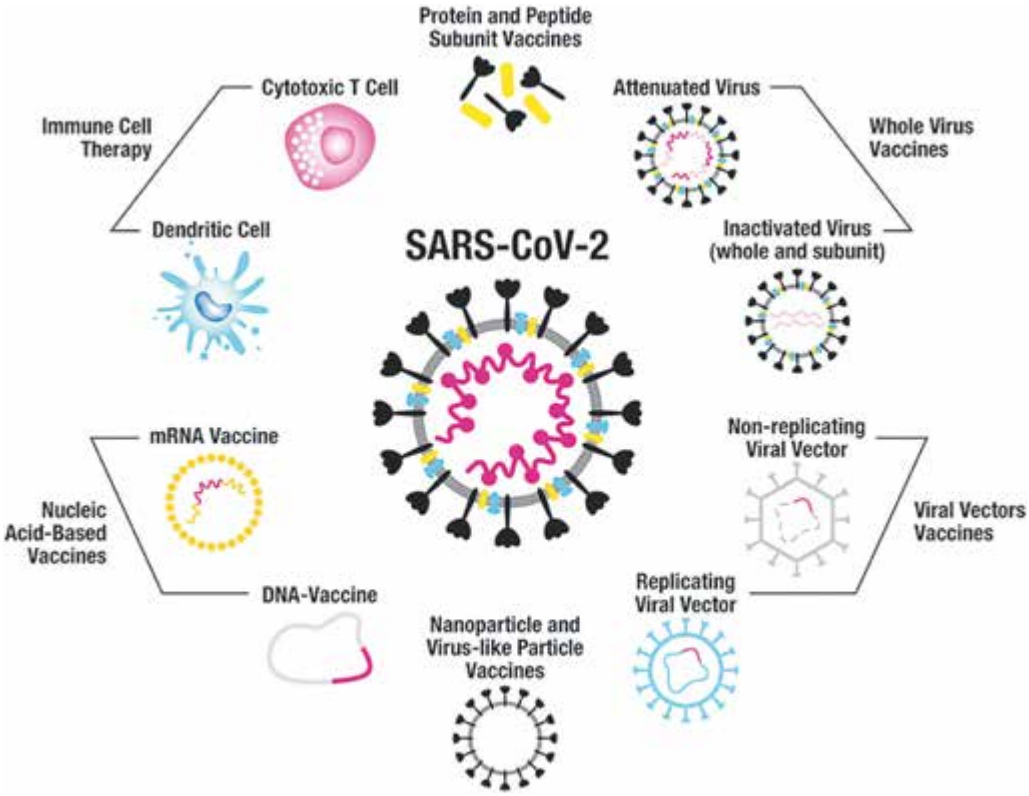

Figure 1.5c Vaccine platforms being employed for SARS-CoV-2. Whole virus vaccines include both attenuated and inactivated forms of the virus. Protein and peptide subunit vaccines are usually combined with an adjuvant to enhance immunogenicity. The main emphasis in SARS-CoV-2 vaccine development has been on using the whole spike protein in its trimeric form, or components of it, such as the RBD region. Multiple non-replicating viral vector vaccines have been developed, particularly focused on adenovirus, while there has been less emphasis on the replicating viral vector constructs. *Source*: K. L. Flanagan, et al. (2020). Progress and pitfalls in the quest for effective SARS-CoV-2 (COVID-19) vaccines. *Front. Immunol.* **11**:579250.

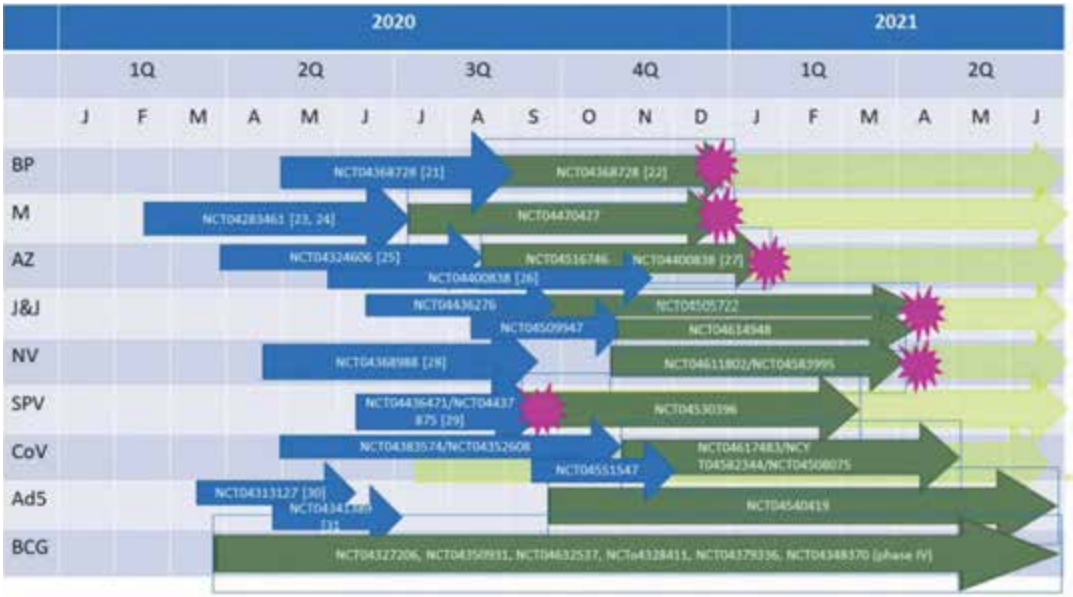

Figure 1.5d Timeline of vaccine production and approval. *Abbreviations*: BP, BioNTech/Pfizer; M, Moderna; AZ, Oxford/Astra Zeneca; J&J, Janssen/Johnson and Johnson; NV, Novavax; SPV, Sputnik V; CoV, CoronaVac; Ad5, Ad5-nCOV; BCG, Mycobacterium bovis. Blue arrows, phase I/II trials; green arrows, phase III trials; yellow arrows, roll out; purple star, (anticipated) approval date. Trial start dates were taken from http://www.clinicaltrials.gov. Approximate end dates of phase I/II trials are the publication dates. End points for unpublished trials are guesses by the author. For the last three vaccines, a guess for an approval date was not possible. Note that all start and end dates of trials, as well as approval dates are approximations. *Source*: B. M. Prüβ (2021). Current state of the first COVID-19 vaccines. *Vaccines* **9**(1):30.

Table 1.1 Major CoVID-19 candidate vaccine platforms in clinical evaluation

Vaccine name	Vaccine platform	Developer	Clinical trial phase	Clinical trial registrations
BNT162b1/ BNT162b2	RNA-based vaccine	Pfizer-BioNTech, Fosun Pharma	Phases I–III in USA, Germany, and China	NCT04368728, NCT04380701, NCT04523571
mRNA-1273	RNA-based vaccine	Moderna, NIAID	Phases I–III in USA	NCT04470427, NCT04405076, NCT04283461
INO-4800	DNA plasmid vaccine	Inovio Pharmaceuticals, International Vaccine Institute	Phases I–III in USA	NCT04447781, NCT04336410
GX-19	DNA plasmid vaccine	Genexine Consortium	Phases I and II in South Korea	NCT04445389

(*Continued*)

Table 1.1 (*Continued*)

Vaccine name	Vaccine platform	Developer	Clinical trial phase	Clinical trial registrations
ChAdOx1 nCov-19 (AZD1222)	Adenovirus vector, non-replicating	University of Oxford, AstraZeneca	Phases I–III in UK, South Africa, USA and Brazil	NCT04324606, ISRCTN89951424, EudraCT2020-001228-32, PACTR202006922165132, EudraCT2020-001072-15
Ad26.CoV2-S	Adenovirus vector, non-replicating	Johnson & Johnson	Phases I–III in USA and Belgium	NCT04436276 NCT04505722 NCT04535453 NCT04509947
Ad5-nCoV	Adenovirus vector, non-replicating	CanSino Biologics Inc., Beijing Institute of Biotechnology	Phases I and II; phase II studies in China and Canada	ChiCTR2000031781, ChiCTR2000030906, NCT04341389 NCT04313127
Gam-COVID-Vac	Adenovirus vector, non-replicating	Health Ministry of the Russian Federation	Phases I–III in Russia	NCT04530396 NCT04436471 NCT04437875
PiCoVacc	Inactivated SARS-CoV-2	Sinovac Biotech	Phases I–III; phase III in China and Brazil	NCT04456595, NCT04383574, NCT04352608
COVID-19 vaccine	Inactivated SARS-CoV-2	Sinopharm, Wuhan Institute of Biological Products Co. Ltd	Phases I–III in China	ChiCTR2000034780, ChiCTR2000031809
BBIBP-CorV	Inactivated SARS-CoV-2	Sinopharm, Beijing Institute of Biological Products Co. Ltd	Phases I–III in China and United Arab Emirates	ChiCTR2000034780, ChiCTR2000032459
SCB-2019	Protein subunit	Clover Pharmaceuticals, GlaxoSmithKline, Dynavax	Phase I in Australia	NCT04405908
NVX-CoV2373	Protein subunit	Novavax	Phases I–III in Australia, USA and UK	NCT04368988 NCT04583995 NCT04533399

Source: C. Wang, Z. Wang, G. Wang, et al. (2021). COVID-19 in early 2021: current status and looking forward. *Sig. Transduct. Target. Ther.* **6**:114.

Another important point is whether asymptomatic individuals can serve as viral carriers. Early data indicate that vaccines will likely help prevent asymptomatic transmission, although most of it is not peer-reviewed. Still, it is worth mentioning. For example, data from the Israeli Health Ministry and Pfizer demonstrated an 89% reduction in both symptomatic and asymptomatic infections

following vaccination while a vaccine trial by Johnson & Johnson found that its vaccines prevented asymptomatic infection in 74% of recipients. Even based on this incomplete picture regarding asymptomatic viral spread, I cannot underscore enough the need for universal vaccination.

1.4.2 Emergence of SARS-CoV-2 Variants

Over time, viruses are prone to mutations of their genomes which arise from random genomic changes as they replicate in an infected person. This results in variants that may have different characteristics than their ancestral strains. Variants pose different concerns of differing degrees. These relate to their: (i) transmissibility (propensity to spread); (ii) virulence (severity of illness); (iii) neutralization capacity (likelihood they will infect people who have recovered from a previous bout of COVID-19), and (iv) potential impact on vaccination through their ability to evade immunosurveillance.

The SARS-Cov-2 genomic RNA is unusually large, the RNA polymerase is error-prone, and mutations accumulate with increasing frequency during infections. With continued uncontrolled viral replication and infection, mutations that give the virus a fitness advantage will emerge. Obviously, SARS-CoV-2 variants[16] that are more virulent or infectious—or both—are of particular concern. According to a few studies, SARS-CoV-2 shares approximately 50–79% of its genetic sequence with MERS-CoV and the first coronavirus, SARS-CoV. Also, interestingly, SARS-CoV-2 shares the receptor-binding domain structure with SARS-CoV.

Monitoring the coronavirus for key mutation(s) in important genomic regions is critical. Most mutations may not affect the virus's virulence or transmissibility because they do not alter the major proteins involved in infection. These are eventually outcompeted by variants with mutations that are more beneficial to the coronavirus. Since the genome sequence of SARS-CoV-2 was first reported in January 2020, thousands of variants have been reported. Most of the genetic and antigenic variations are innocuous and do not contribute to enhanced virulence or infectivity. However, the emergence of a few, referred to as variants of concern (VOCs), have caused considerable consternation. Generally, VOCs have one or more mutations that confer worrisome epidemiologic, immunologic, or pathogenic properties. The B.1.1.7 lineage (or VOC 202012) variant was the first VOC described in the UK in late December 2020 (Fig. 1.6). This variant is considerably more contagious than the original virus and recent evidence indicates that infection with this B.1.1.7 variant also comes with an increased risk of severe illness and death. A second variant, the B.1.351 lineage (or 501Y.V2) was reported in South Africa in late 2020. A third VOC, B.1.1.248/B1.1.28/P1 (or 501Y.V3), was reported in Brazil in early January 2021. As of May 2021, all three variants have been found in the US. A fourth variant, the 20A.EU1 variant,

[16]During replication, a virus often undergoes genetic mutations that may create what are called variants (sometimes referred to as strains). Some mutations weaken the virus while others may yield some advantage that enables the variants to proliferate. A variant that deviates significantly from its viral ancestors may be identified as a new lineage, or branch on the evolutionary tree.

first identified in Spain, contains a mutation called A222V on the viral spike protein. According to the WHO, another VOC, labeled the B.1.617 variant, has become the dominant strain across India. Evidence is growing that this variant might be more transmissible and slightly better at evading immunity than the existing variants.

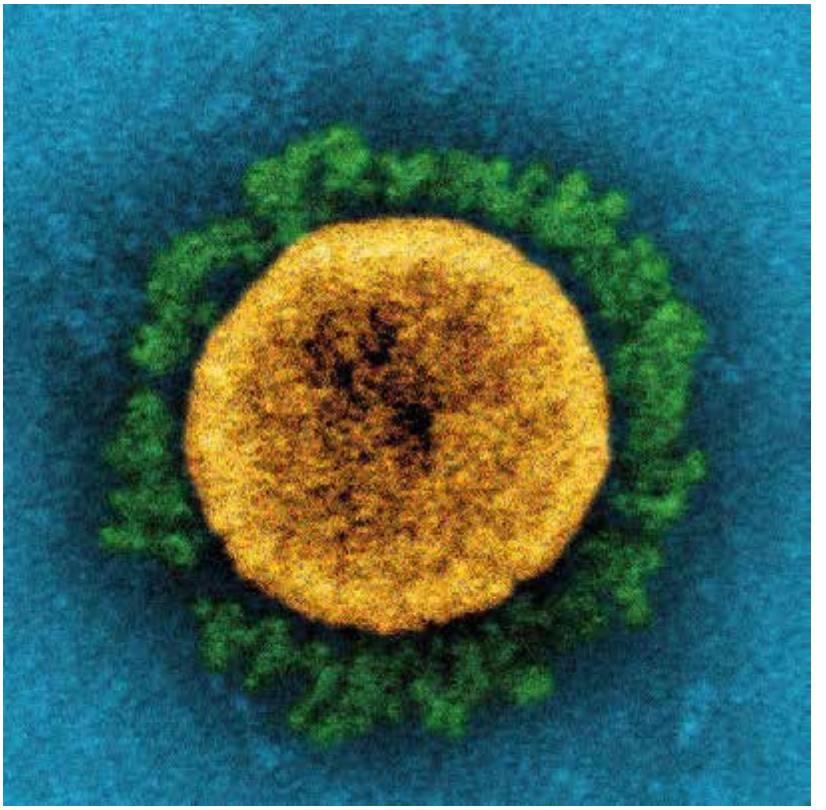

Figure 1.6 False-color transmission electron micrograph of a SARS-Cov-2 B.1.1.7 variant. A single virus particle is shown (yellow). The variant's increased transmissibility is believed to be due to changes in the structure of the spike proteins (green). Image captured at the NIAID Integrated Research Facility in Fort Detrick, Maryland. *Courtesy of NIH.*

I am skeptical if vaccine companies can develop new vaccine versions promptly prior to the emergence of deadlier second and third generation variant waves. In my view, genomic surveillance is key here as it serves as an early warning system that can detect threatening mutations before they become more widespread. Furthermore, genetic variations in a virus can render diagnostic tests ineffective.[17] What makes the future of this virus so hard to predict is that it is not just the individual mutations that matter, but also the order and combinations in which

[17]For molecular tests, their sensitivity and specificity depend on the number and location of genes that the test targets. Most antigen-based tests should continue to work as most are targeting the N antigen of the virus, a region that has so far remained conserved in the variants. But this can change in the near future.

they occur. *Will SARS-CoV-2 retain its ability to cause enhanced infection and virulence as it mutates further and more people gain immunity through infections or vaccines?*

1.5 Will We Ever Achieve Herd immunity?

Achieving herd immunity (Box 1.1; Fig. 1.7) requires vaccination (or natural infection). According to few estimates and my own calculations, given the various variants of SARS-CoV-2, we may need a vaccination rate of 80–90% if some degree of normalcy is desired. A tremendous effort will be required to achieve such high vaccination rates. This would mean that all adults and adolescents in the US will have to be fully vaccinated to approach 80% vaccination—a high bar indeed. Is it possible? I am not sure if this herd immunity threshold will ever be attainable. Here in the US, daily vaccination rates are slipping, viral variants are emerging, poor infectious disease management policies are reappearing, and many pandemic restrictions are being relaxed prematurely.

Global distribution of the COVID-19 vaccine has been lopsided.[18] So far, in July 2021, major populations like India have only fully vaccinated 4.1% of their populations while here in the US the vaccination rate currently stands ~48%. BBC reports that as of March 2021, 80% of the vaccines have been administered to the developed nations while only 20% have gone to the developing nations. According to data collected by Bloomberg, as of May 29, 2021, countries/regions with the highest incomes are getting vaccinated more than 30 times faster than those with the lowest. In fact, data shows that more than 1.84 billion doses have been administered around the world—enough to only fully vaccinate 12% of the global population. As discussed above, this is still a far cry from what will be needed for herd immunity and to minimize emergence of virulent novel variants. A failure to vaccinate much of the developing world will leave a large reservoir of circulating virus, giving it the chance to mutate and spill over to developed countries.

Another important point to remember is that it is hard to achieve our goal of herd immunity in the absence of vaccinations to infants and young people. By focusing solely on adult vaccination R&D, we have left out the vulnerable, immunologically naïve ~25% of the population that still have no available shots: kids. In my view, a pediatric vaccine for the disease is an urgent global health priority and the time for that to happen is now. This is especially true since we have substantial safety data from adult vaccine R&D, clinical trials, and field use. Vaccines given to kids will not only help curb the spread of SARS-CoV-2 but also protect young people who are at high risk. Big pharma is finally turning its attention towards this important demographic and clinical trials in adolescents or young children are underway.

[18]The COVID-19 Vaccines Global Access (COVAX) Facility, a nonprofit, is purchasing shots in bulk at a discount and distributing them to the world's most resource-strapped countries.

Box 1.1 What is herd immunity?

Herd immunity, sometimes called community immunity, is the indirect protection from an infectious disease that occurs when a high percentage of population is immune either through vaccination and/or immunity developed through previous infection. Theoretically, this makes the spread of the infectious disease from person to person unlikely. Herd immunity protects the most vulnerable members of the population (babies who have not received vaccinations, pregnant women, the immunocompromised or those on immunosuppressive drugs). Unlike the unethical and rash approach of Sweden, herd immunity against COVID-19 should be achieved through vaccination, not by exposing the population to the virus. Achieving herd immunity via vaccines makes diseases rarer and saves lives. On the contrary, letting COVID-19 spread through populations, of any age or health status will lead to unnecessary infections, suffering, and death. To safely achieve herd immunity a substantial proportion of a population would need to be vaccinated, lowering the overall amount of virus able to spread in the whole population. Although the proportion of the population that must be vaccinated against SARS-CoV-2 to begin inducing herd immunity is unknown, I believe that it could be as high as 85–90%. This means that about 85–90% of a population will need to be vaccinated while the remaining 10–15% will be protected by the fact that COVID-19 will not spread among those who are not vaccinated.

There is also enormous confusion, disagreement, lack of scientific knowledge, and conflicting information pertaining to the delivery, use, and safety of COVID-19 vaccines. For instance, according to the latest official guidance from the CDC, pregnant women who are health-care personnel or essential workers "may choose to be vaccinated." The major problem is that there is hardly any data available on COVID-19 vaccine safety with respect to pregnant women, given that they were excluded from clinical trials as has historically been the case. According to the CDC and the FDA, preliminary data from their safety monitoring systems did not identify any safety concerns for pregnant women who were vaccinated or for their babies. Two recent research studies[19] (not clinical trials) show that the two COVID-19 mRNA vaccines currently available in the US appear to be safe and effective in pregnancy, with the potential to benefit both mother and baby. In my view, more data derived from robust clinical trials is warranted.

[19]A. Y. Collier, et al. (2021). Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA* e217563, doi: 10.1001/jama.2021.7563; E. D. Shanes, et al. (2021). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in pregnancy: Measures of immunity and placental histopathology. *Obstet. Gynecol.*, doi: 10.1097/AOG.0000000000004457.

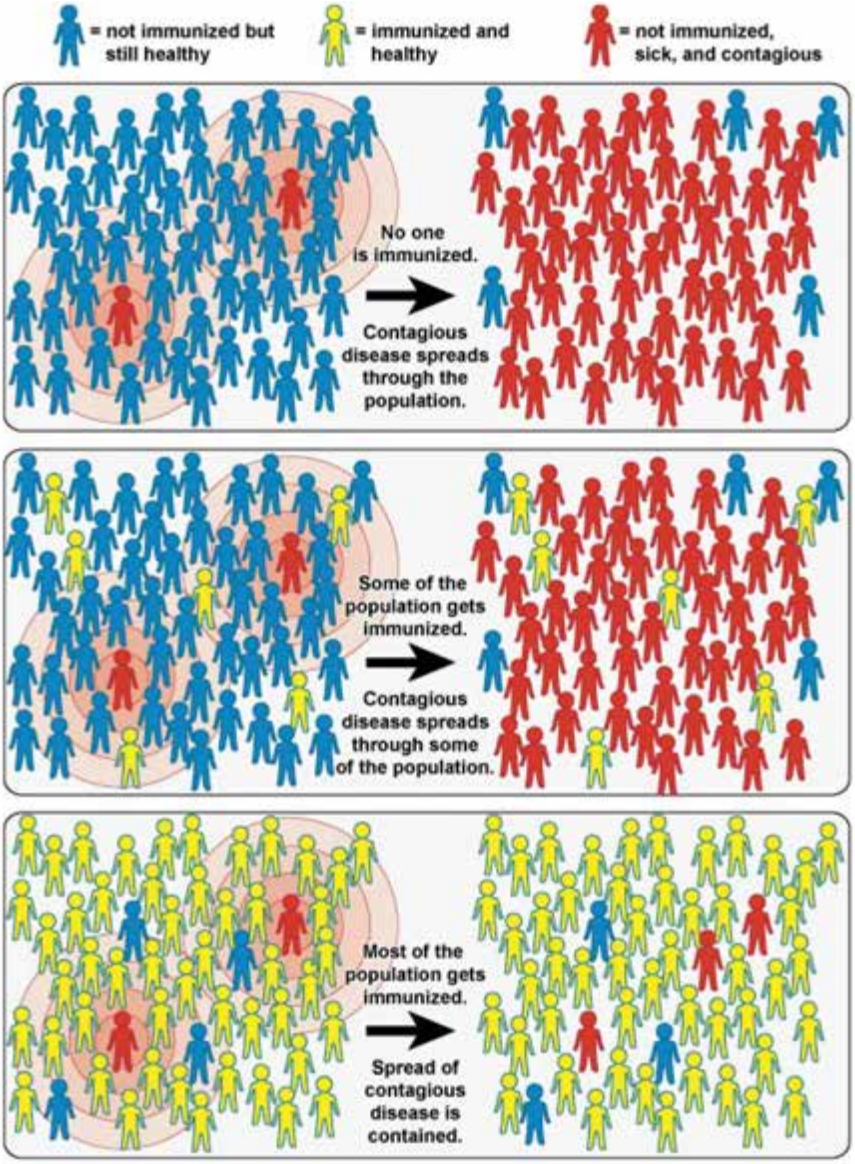

Figure 1.7 Building the herd: The concept of herd immunity. When a critical portion of a community is immunized against a contagious disease, most members of the community are protected against that disease. The principle of community immunity applies to control of a variety of contagious diseases, including influenza, measles, mumps, rotavirus, and pneumococcal disease. The top box depicts a community in which no one is immunized, and an outbreak occurs. In the middle box, some of the population is immunized but not enough to confer community immunity. In the bottom box, a critical portion of the population is immunized, protecting most community members. *Legend*: not immunized, healthy immunized, healthy not immunized, sick, and contagious. *Courtesy of Tkarcher, CC BY-SA 4.0 via Wikimedia Commons*.

1.6 Patents and COVID-19

Waiving vaccine patents to evenly manufacture and distribute COVID-19 vaccines (and other therapeutics) around the world is a hotly debated topic in June 2021. This gained increased traction following the explosion of cases and deaths in India in May 2021. The easing of patent protections is essential in a pandemic. The campaign was initiated by India and South Africa, and is being backed by more than 100 countries, the WHO, UNAIDS, etc. The US has joined in and supports a waiver on intellectual property for COVID vaccines, even though big pharma and most developed countries do not support it. I consider this a historic move. As a patent agent for the past two decades, I prefer compulsory licensing over outright patent waivers. However, the scope of the current pandemic makes waivers appropriate. In addition to waivers, patent pooling is also an excellent mechanism to pool our global intellectual property resources and is suggested by many[20]: "We call on pharmaceutical companies to contribute to a pool of patents set up by the World Health Organization (WHO). That will speed up the manufacture of generic, affordable COVID-19 vaccines and treatments while protecting firms' incentives to invest in future research … The practice of pooling patented technologies to produce medicines already occurs for HIV, hepatitis C and tuberculosis treatments. Fees are typically lower when licenses are negotiated as a bundle with generics producers, implying increased volume. Yet firms can anticipate extra revenue from participation in a voluntary pool, and thus be more willing to maintain innovation and share know-how than with compulsory licensing."

1.7 Vaccine Passports: Another Bad Government Idea

They that can give up essential liberty to obtain a little temporary safety deserve neither liberty nor safety.

—Benjamin Franklin, *Historical Review of Pennsylvania*, 1759

No culture can live if it attempts to be exclusive.

—Mahatma Gandhi

Jurisdictions in the US and around the world are handling the current pandemic in variety of ways. Some are enforcing mask mandates while others are passing laws where masks cannot be forced upon a person. Some are using contact-tracing applications and systems to conduct "viral surveillance" while others are passing laws that grant citizens complete freedom to decide if they should participate in such programs. Some issue stringent requirements for social distancing while others forbid such actions. Some are passing regulations about self-isolation and quarantines while others are not. The list goes on and on. In essence, we have a maze of confusing policies, along with protests, dissent,

[20]E. B. de Villemeur, et al. (2021). Pool patents to get COVID-19 vaccines and drugs to all. *Nature* **591**:529.

shutdowns, riots, pandemic fatigue, and fear. In this crisis, we have to balance competing legal, ethical, medical, privacy, and moral principles. Easier said than done. In this backdrop, I discuss below the concept of "vaccine or immunity passports," and why they are a bad idea.

Immune response to SARS-CoV-2 is a complex topic. For instance, an immune response to the live virus is different from the response to a single viral protein introduced via a vaccine. And then there are those who have been vaccinated following COVID-19. Our knowledge regarding the humoral immune response to SARS-CoV-2 has been rapid, though areas of uncertainty persist. We are a long way from understanding the characteristics of the antibody response, its dynamics over time, its determinants, and the immunity it confers to different age groups and disease. On the other hand, relatively less is known about cell-mediated immunity to SARS-CoV-2. We are slowly learning more. For example, a recent report[21] demonstrated that blood levels of antibodies fall sharply following acute infection, while memory B cells remain quiescent in the bone marrow, ready to act as needed.

In any case, clinical, policy, and economic implications will be greatly driven by our knowledge of the immunology of SARS-CoV-2. These include the proposed use of an "immunity passport" or a "risk-free certificate,"[22] a form of certification for individuals with positive detection of antibodies that can enable them to avoid quarantine, and allow them to travel or to return to work. The assumption is that they are protected against reinfection. But, what about reinfection from variants that are undetectable via current tests? What about reinfection from an asymptomatic carrier state following infection?

The idea is being floated in Germany, the United Kingdom, and other nations. Australia, Denmark, and Sweden have committed to implementation; and Israel is already issuing "green passes" to vaccinated residents. Hungary has introduced a policy allowing people to enter the country if they can provide evidence that they have already recovered from COVID-19. Iceland is planning on introducing a similar policy that will allow people who have already had COVID-19 to be exempt from the nationwide mask mandate. The European Union plans a "Digital Green Certificate" enabling free travel within the bloc. Although travel eligibility has been the primary focus here, some use these certificates to regulate access to social events, recreational activities, sporting arenas, theatrical performances, and more. New York's "Excelsior Pass" permits attendance at theaters, arenas, event venues, and large weddings. Airlines could soon introduce "vaccine passports" to facilitate international travel.

Currently, in this evolving pandemic, the issue of immunity passports is a poor proposal given the uncertainties relating to COVID-19 immunity. There is simply not enough evidence about the effectiveness of antibody-mediated immunity

[21]J. S. Turner, et al. (2021). SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. *Nature*, https://doi.org/10.1038/s41586-021-03647-4.

[22]Technically, any documentation that proves a full dose of COVID-19 vaccination can be considered a vaccine passport. Presently, yellow fever is the only disease indicated in the International Health Regulations for which nations may require vaccination proof as a condition for entry. Obviously, WHO can recommend (via advisories) that countries require vaccination proofs.

to guarantee such certification.[23] As discussed earlier, the data is incomplete on asymptomatic spread in vaccinated individuals. Such certificates falsely assume that a second infection will not occur if a person has recovered from COVID-19, has had a positive COVID-19 test, or has been vaccinated. Immunity passports also raise ethical, legal, and practicality issues, doubtful economic benefits, privacy concerns, and the risk of discrimination. In fact, they may lull individuals into a false sense of security, leading them to ignore public health advice and increasing the risks of continued viral spread. Even if immunity passports were limited to health-care personnel, the number of tests required would be unfeasible. Many respectable health organizations, medical societies, religious leaders, and medical editors have opposed vaccine passports.

1.8 COVID-19 Testing

You're paying billions of dollars in this very inequitable way to get the most worthless test results of any country in the world. No other country has this testing insanity.

—Bill Gates

In February 2020, the FDA began authorizing tests to diagnose active COVID-19 infections. During a crisis, the FDA can grant an emergency use authorization (EUA) for medical products using a lowered approval standard rather than the full approval based upon more extensive evidence. According to the FDA: "The EUA process is different than FDA approval, clearance, or licensing because the EUA standard requires less evidence than the full approval, clearance, or licensing standard. Under an EUA, the data must show that a product may be effective and that the known and potential benefits outweigh the known and potential risks. This enables the FDA to authorize the emergency use of medical products that meet the criteria within days or weeks rather than months to years. The FDA has prioritized review of EUA requests for tests where authorization would increase testing accessibility (such as point-of-care (POC) tests, home collection tests, and at-home tests) or would significantly increase testing capacity (such as tests that reduce reliance on test supplies and high-throughput, widely distributed tests)."

Serology tests (i.e., antibody testing) are critically important for virus outbreaks. Also, it is important that national and international regulatory agencies like the FDA and EMA not approve substandard serology tests to be marketed or unauthorized products to appear in the marketplace. Unfortunately, this did happen and made viral testing confusing and unreliable. This reflected the broader problem with governments who were ill equipped to handle a pandemic. Clearly, they lacked a coordinated preparedness plan and there was over reliance on their antiquated regulatory system, or they approved COVID-19 tests

[23]As of the June 2021, there is no conclusive data that establishes with certainty that the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infections. I strongly believe that we will require booster shots periodically.

under extreme political and public pressure. Maybe, it would be helpful to be proactive and evaluate test performance prior to global microbial outbreaks? *A common approach to validating test design and performance is urgently needed and federal governmental agencies need to step up their game in this regard. Independent assessment of molecular diagnostic, antigen, and serology test accuracy is needed. Along with this, test developers and biomedical researchers should receive robust and coordinated assistance from national and international mechanisms in obtaining patient specimens or other clinical samples to validate their tests.*

Table 1.2 Coronavirus disease 2019 testing basics: comparing diagnostic and antibody tests. *Courtesy of the FDA.*

There are two different types of tests – diagnostic tests and antibody tests.

Diagnostic tests can show if you have an active Covid-19 infection and need to take steps to quarantine or isolate yourself from others. **Molecular** and **antigen tests** are types of diagnostic tests than can detect if you have an active COVID-19 infection. Samples for diagnostic tests are typically collected with a nasal or throat swab, or saliva collected by spitting into a tube.

Antibody tests look for antibodies in your immune system produced in response to SARS-CoV-2, the virus that causes COVID-19. **Antibody tests should not be used to diagnose an active COVID-19 infection.** Antibodies can take several days or weeks to develop after you have an infection and may stay in your blood for several weeks or more after recovery. Samples for antibody tests are typically blood from a finger stick, or blood drawn by your doctor or other medical personnel.

	MOLECULAR TEST	ANTIGEN TEST	ANTIBODY TEST
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification test (NAAT), RT-PCR test, LAMP test	Diagnostic test, viral test, rapid test	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal swabs, either shallow or deep (most tests). Saliva (some tests)	Nasal or nasopharyngeal swab (most tests)	Blood from a fingerstick or vein
How long it takes to get results...	Less than an hour (at-home tests and some point-of-care locations), same day (some point-of-care locations) or 1-3 days (tests sent to a lab for processing). Some tests may take longer in some locations, depending on testing capacity.	Some may be very fast (15–30 minutes), depending on the test	Same day (some point-of-care locations) or 1-3 days (tests sent to a laboratory for processing)
Is another test needed...	Not usually. This type of test is typically highly accurate andmusually does not need to be repeated. Some may indicate the need to re-test in certain circumstances.	Maybe. Positive results are usually highly accurate, but false positives can happen, especially in areas where very few people have the virus. Negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Shows if you've been infected by the virus that causes COVID-19 in the past
What it can't do...	It cannot show if you ever had COVID-19 or were infected with the virus that causes COVID-19 in the past	It may not detect an early COVID-19 infection. Your health care provider may order a molecular test if your antigen test shows a negative result, but you have symptoms of COVID-19. It also cannot show if you ever had COVID-19 or were	It cannot diagnose COVID-19 at the time of the test or show that you do not have COVID-19

No test can ever be 100% accurate. Any COVID-19 test's performance will vary and is based on disease prevalence in the tested population. In fact, diagnostic tests may be less accurate in populations with a low prevalence of disease and in asymptomatic individuals, individuals who shed little virus, or individuals who are early or late in the course of illness. We all know that tests are rated on their sensitivity and specificity. In simple terms, sensitivity of a test is defined as the fraction of positive cases that the test correctly identifies as positive, and specificity of a test is defined as the fraction of negative cases that the test correctly identifies as negative. A highly sensitive test will generally have a low false negative rate but will run a risk of false positives if the test's specificity is low. A highly specific test will generally have a low false positive rate but will run a risk of false negatives if the test's sensitivity is low. To reduce the risk of false negative results, it is important to perform the test in accordance with its authorization and as described in the authorized labeling. To mitigate the false results, most COVID-19 tests are ordered by clinicians and are prescription-only so that the results can be interpreted for patients. Any tests authorized for non-prescription use (i.e., direct-to-consumer (DTC) or over-the-counter" (OTC) use), directs patients to consult their health-care provider for result interpretation. There are two different types of tests—diagnostic tests and antibody tests, as discussed in Table 1.2 and Fig. 1.8. The latest guidance (dated May 13, 2021) for antigen testing for SARS-CoV-2 is available on the CDC's website (https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html).

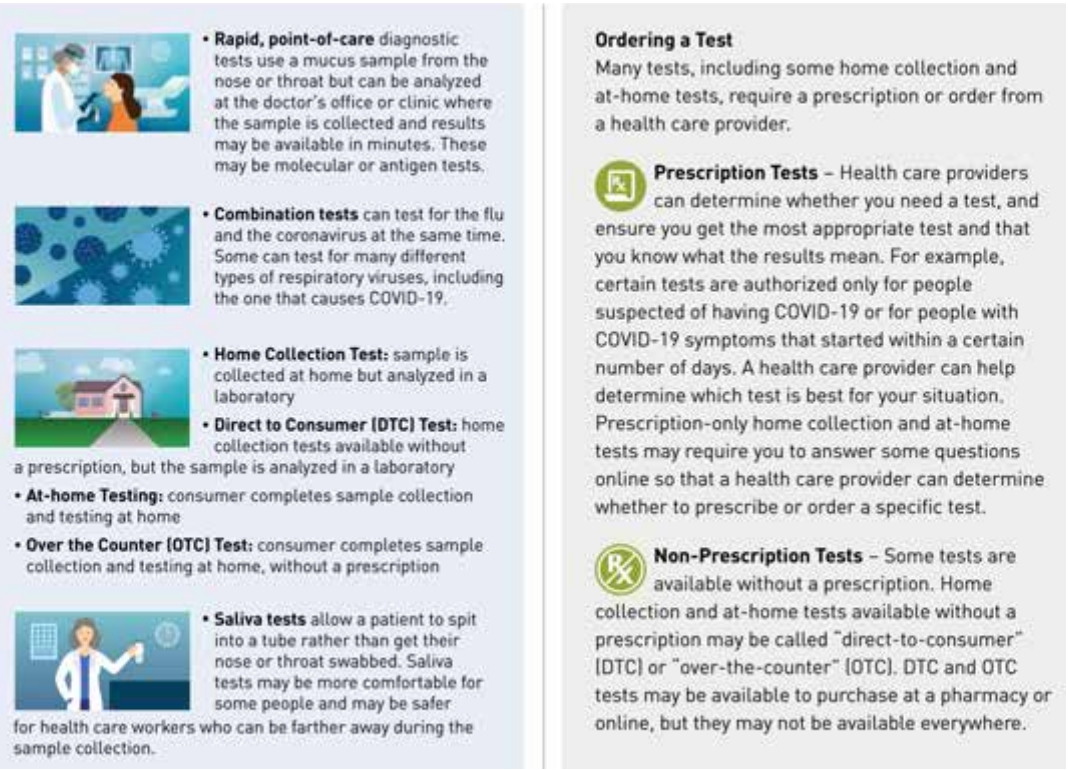

Figure 1.8 Diagnostic tests with alternative options. *Courtesy of the FDA.*

One of the most important aspects of COVID-19 testing centers around interpretation of results. In fact, there are problems with interpretation of serology test results to inform patient care. These problems continue to this day. Again, the role of federal agencies is paramount here as well. The misuse of serology tests for diagnosis; the potential for false positive results when a single test is used in populations with a low rate of infection; and the perception of immunity can all result in a skewed picture of the pandemic. This leads not only to misdiagnosis but also imposition of improper quarantine and other restrictive measures.

1.9 COVID-19 Convalescent Plasma: Is There a Benefit?

I need hardly add that the fight against cattle tuberculosis only marks a stage on the road which leads finally to the effective protection of human beings against the disease.

—Emil Adolf von Behring, Nobel Lecture, 1901

Intravenous human immunoglobulin delivery for prophylaxis and treatment is well known for numerous microbial diseases. Passive immunotherapy[24] has been used since the late 19th century. In fact, the first Nobel Prize to von Behring in 1901 was awarded for passive serum therapy (immune serum containing neutralizing antibodies) for patients with diphtheria. During the Spanish Flu of 1918, serum from convalescent (recovered) patients was used. Similarly, its use is advocated for the treatment of patients with COVID-19.[25] The idea is to give convalescent plasma to an infected patient (i.e., that person is getting antiviral antibodies) because it may take weeks to produce his/her own antibodies while the virus can continue replicating unchecked. Convalescent plasma ("survivor's plasma") can be used for prophylaxis of high-risk people before they get infected or for treatment of patients who are *already* infected but are not fighting the virus well. Plasma harvested from convalescent COVID-19 patients, containing antibodies against SARS-CoV-2, can be used in two ways (Fig. 1.9). The primary proposed protective mechanism here is neutralization, via the delivery of antibodies, although antibody-dependent cellular cytotoxicity and phagocytosis may also play a role.

I wish to point out that despite what the FDA says, use of convalescent plasma therapy against SARS-CoV-2 is not a simple or straightforward issue[26]: "At this time, convalescent plasma should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well. Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be

[24]On the other hand, vaccination therapy is a form of active immunotherapy.

[25]More than 100,000 people in the United States and many more worldwide have already been treated with it since the pandemic began.

[26]L. M. Katz. (2021). (A little) clarity on convalescent plasma for COVID-19. *N. Engl. J. Med.* **384**(7): 666–668.

discouraged, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU."

In my view, antibody cocktails in test tubes can never be equated to vaccines for a variety of reasons, including the effectiveness of the latter in priming humoral and cellular arms of the immune system. Also, there is data that antibody cocktails, such as those currently being tested by Regeneron and Eli Lilly, may be less effective against mutations present in the B.1.351 variant of SARS-CoV-2. Several published randomized controlled trials were halted early due to concern regarding a lack of benefit, low enrollment, or the finding that most recipients had baseline neutralizing antibodies with similar titers to the donors. In March 2021, the NIH halted a clinical trial evaluating the safety and effectiveness of COVID-19 convalescent plasma in treating emergency department patients who developed mild to moderate symptoms of COVID-19.

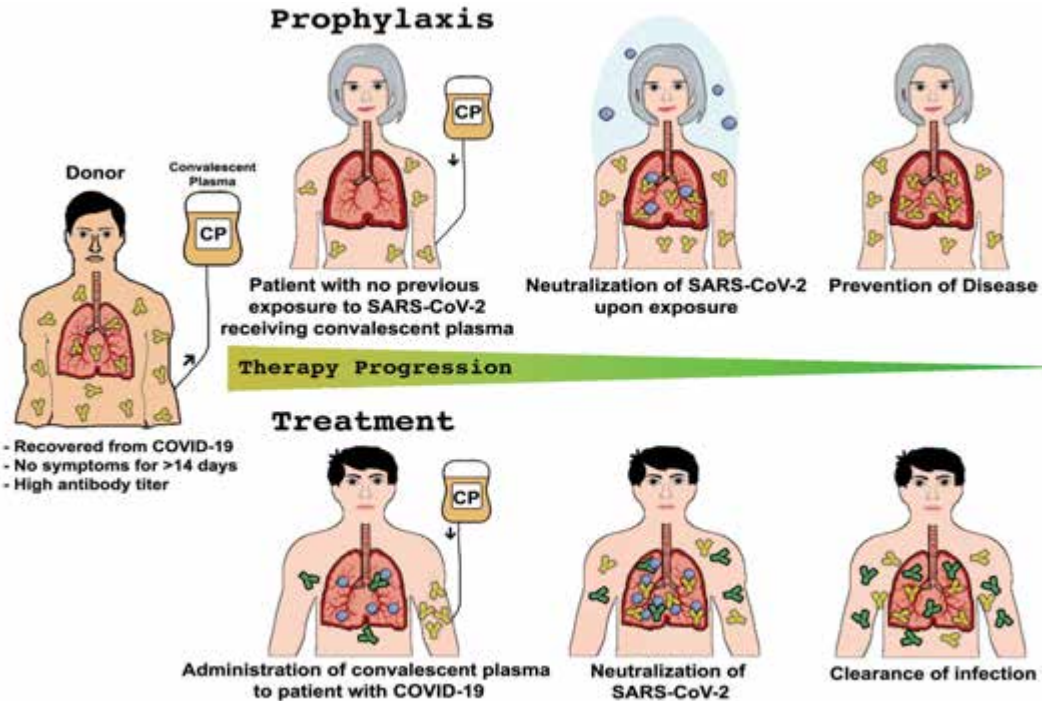

Figure 1.9 Overview of the use and applications of convalescent plasma therapy. *Source*: D. Montelongo-Jauregui, et al. (2020). Convalescent serum therapy for COVID-19: a 19th century remedy for a 21st century disease*. PLoS Pathog*. **16**(8):e1008735.

1.10 Looking Back and Moving Forward: Will We Win?

… have the infectious diseases that we observe today always existed? Or have some of them appeared in the course of history? Can we assume that new ones will appear? Can we assume that some of these diseases will disappear? Have some of them already disappeared? Finally, what will become of humanity and domestic animals if, as a

result of more and more frequent contacts between people, the number of infectious diseases continues to increase?

—Charles Nicolle, *Destin des maladies infectieuses,* 1933

Alone we can do so little; together we can do so much.

—Helen Keller

The final trajectory of the pandemic is impossible to predict given that our track record for eliminating viruses has been a poor one. Wuhan, China, was ground zero for SARS-CoV-2 but now we are in this together and to survive we will need a concerted effort. Disease spread is inevitable in our interconnected world. In fact, for decades experts have warned us of impending danger, recommended setting surveillance programs to recognize emerging/reemerging microbes, and proposed methods of intervention.[27]

Ending, or at least stabilizing, the current pandemic and addressing future public health emergencies should be the focus. How people and health systems respond to the current pandemic will be key, not only to planning for and protecting from emerging microbes of the future, but for maintaining economic and political stability for the 2020s and beyond. Public health infrastructures, big pharma, a wealth of drugs, hospitals, health-care providers, and scientists, all have fared poorly to contain this pandemic. The volatile mix of politics (Box 1.2), globalization, national rivalries, inept health organizations, misinformation, arrogance, and ignorance all fueled the development and spread of COVID-19. In the critical early phases, nations failed to implement basic infectious disease control management measures such as data gathering, testing, contact tracing, quarantines, and distribution of critical medical supplies to health-care providers.

Box 1.2 COVID-19 and politics: disarray, blame, and mismanagement

The highly politicized response to the pandemic did not help. Politicians certainly share a major portion of blame for the pandemic and its perpetuation. Political leaders either failed to follow established basic pandemic-response plans or never fully and reliably funded existing pandemic plans. The haphazard and disjointed approach of political leaders and health-care organizations shows how miserably they have failed in addressing the seriousness that this microbe poses with respect to its impact on society, political stability, and the economy. We have so much talent and brilliance on this planet, yet it is stifled by politicians, religious leaders, and fanatics. Societal divisiveness and political upheaval continue to cause us to stumble

(*Continued*)

[27] J. Lederberg, R. E. Shope, and S. C. Oaks, Jr. (1992). *Emerging Infections: Microbial Threats to Health in the United States.* National Academies Press, Washington, DC. M. S. Smolinski, M. A. Hamburg, and J. Lederberg. (2003). *Microbial Threats to Health: Emergence, Detection, and Response.* National Academies Press, Washington, DC.

Box 1.2 (*Continued*)

as we struggle to convince citizens to get vaccinated or follow the latest guidelines. This dangerous trajectory is likely to continue for years. Coordinated preparation and action was critical. Instead, government leaders, healthcare organizations, and society failed to provide an effective response. Demands for freedom pushed aside commonsense approaches crucial to tackling a serious infectious microbe.

The misinformation pandemic has created confusion. Objectivity and fairness in journalism has been supplanted by "opinion news," championed by cable-news networks like CNN, Fox News, and others. Inaccurate reporting of the pandemic has been costly with lives lost here at home and throughout the world. It is dangerous to have self-annotated experts provide viewpoints rather than medical facts.

Many political leaders from Britain to Brazil to India ignored advice of their own health advisors. They found political gain more expedient. They continued to hold vast rallies at super spreader events. They even belittled those who were seriously ill with COVID-19. Some of them spun the pandemic to shine a spotlight on themselves and highlight their own perceived achievements. Authoritarians and politicians always seize the megaphone for themselves. A classic example is that of "Dr." Andrew M. Cuomo, the now disgraced governor of New York state, who gave daily briefings and PowerPoint presentations on TV. He authoritatively ticked through the latest statistics on infections, hospitalizations, nursing homes patients, and deaths—all sprinkled with medical errors and politics. Many called it "The Andrew Cuomo Show." It was especially painful for me to watch this arrogance on display while my helpless 85-year-old mother languished in a private nursing home in New York state, whose health department had lost control over the pandemic along with nursing home data. It was clear that this corrupt politician only cared about his ratings and image.

Health-care agencies tasked with springing into action during a pandemic have also been in disarray and not fared much better than the politicians that controlled them. The WHO correctly received poor marks and harsh criticism for its passivity in the face of the pandemic. Since the Centers for Disease Control and Prevention failed miserably in the early phase of the pandemic and played a side role, some labeled it the "Centers for Disease Observation." The FDA was a mess as well with the rollout of its COVID-19 testing. It became clear that a large proportion of COVID-19 negative results were inaccurate ("false negatives") because of an issue inherent in the tests' design resulting from inadequate regulatory reviews.

Handling a pandemic in a decentralized manner where local politicians dictate events is not an ideal approach. However, this is the flaw that we must endure in a democracy where government power is not concentrated and there is a patchwork of decentralized mechanisms to address pandemics. Microbes do not recognize boundaries, timelines, politics, or policies, but rather feed on chaos, arrogance, global conflicts, confusion, and divisiveness.

The disastrous start with inaccurate and chaotic testing has continued with vaccination rates far below what would be considered as potentially rendering herd immunity. Due to globalization, the risk of pandemics is shared by the entire planet, but vaccines, testing, and therapeutics remain prioritized to exclusive, usually wealthy nations. Obviously, while it may make us feel safer here in the US, variants from the developed world will evolve further and infect the globe. This is likely to reduce efficacy or render useless the current generation of vaccines here.

So, have we learnt any lessons? One is the need for integration between science and policy. Another is that accurate dissemination of information to the public is essential. Trust is the primary currency of good crisis communication and political leaders quickly lost trust with inaccurate, untimely, inconsistent policies, and information. In a foreshadowing of COVID-19 outbreaks all over the world, health-care systems and facilities were completely overwhelmed. Unfortunately, this vicious cycle continues to play out as the pandemic roars on from one epicenter to another. A flattening of the curve in one region will lead to a peak elsewhere. Today we may rejoice lowered infections here in the US only to repent a spike in the months to follow, only this time the attack may be with virulent variants. An epidemic in one spot may morph into a pandemic in another area. Hopefully, we will not become complacent as we feel secure and consider this someone else's problem. Our track record is poor as after each disease threat faded, so did urgency and governmental funding. Flexible adaptation is key to managing pandemics. What is a great approach today may need to be modified or discarded tomorrow in favor of policies that are more sensible. A reasonable leeway for balancing protection of public health with a return to pre-pandemic life is essential, though I am doubtful that we will ever return to pre-pandemic normalcy. In my view, here and abroad, we will continue to face a patchwork of ineffective policies, poor contact tracing efforts, and inequitable vaccination rates, as novel variants evolve.

Let us not lose sight of the fact that while we may be far from others in distance and perspective, we are brought nearer in our common conflict with this deadly nanoparticle, the SARS-CoV-2. This is a story of humanity, of fear and resignation, of compassion and dilemma, of persistence and hope. As global citizens, the pandemic has made painfully real our interconnectedness while also strengthening us with the many acts of kindness and compassion that serve as a uniting thread.

The solutions for pandemic control are well-known, based on lessons from the past. They include adequately investing in public health systems to detect early signs of a microbial outbreak; ensuring that public and private labs collaborate on testing, tracing, and quarantining people exposed to an infection; ensuring an adequate supply of facilities (hospital beds, personal protective equipment, drugs, health-care staff, and medical supplies); and investing in an efficient R&D infrastructure to develop, scale up, and distribute vaccines and therapeutics.

Declaring hollow victories, issuing vaccine passports, ignoring contact tracing, or hoarding vaccines and therapeutics will not ensure global safety, slow viral

transmission, or prevent virulent mutants from evolving. In fact, all these poor approaches will have the exact opposite effect. A viral wave elsewhere today will arrive as a spike here tomorrow. I am certain that virulent microbes will continue to evolve from their zoonotic reservoirs and jump to humans. This reality must spur everyone—lawmakers, big pharma, citizens, regulatory agencies, global health organizations, biomedical researchers, physicians—to examine what went wrong again and create a more workable plan for future outbreaks.

After all, alone we can do so little, together we can do so much. After all, we are all in this together.

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