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SARS-CoV-2 Is Not Special, but the Pandemic Is: The Ecology, Evolution, Policy, and Future of the Deadliest Pandemic in Living Memory

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Keywords

SARS-CoV-2, spillover, mitigation, social adversity, host pools, viral evolution

Abstract

The COVID-19 pandemic is extraordinary, but many ordinary events have contributed to its becoming and persistence. Here, we argue that the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which has radically altered day-to-day life for people across the globe, was an inevitability of contemporary human ecology, presaged by spillovers past. We show the ways in which the emergence of this virus reiterates other infectious disease crises, from its origin via habitat encroachment and animal use by humans to its evolution of troublesome features, and we spotlight a long-running crisis of inequitable infectious disease incidence and death. We conclude by describing aspects of SARS-CoV-2 and the COVID-19 pandemic that present opportunities for disease control: spaces for intervention in infection and recovery that reduce transmission and impact. There are no more "before times"; therefore, we encourage embracing a future using old mitigation tactics and government support for ongoing disease control.

INTRODUCTION

Over 6 million people have died of COVID-19 infection in less than 3 years. Highly transmissible, frequently manifesting with weak uncoordinated symptoms or asymptomatically, and a stealthy escapee of evolved mammalian immune tactics, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is by any standard an incredibly successful pathogen. However, as far as pathogens go, it is not special and that is a big problem for the future of human health. Rather, the circumstances of SARS-CoV-2's emergence tied to habitat use and encroachment by humans and the virus's pandemicity, increasing transmissibility, and patterns of severity repeat well-worn patterns of zoonoses past. Like other pathogens before it, SARS-CoV-2 is also an agent of disability, and its burden is deeply uneven, with those who are economically marginalized or racialized suffering greater impact. The success of SARS-CoV-2 is due in part to an inheritance of ancient adaptations that allow it to escape or dismantle multiple immune checkpoints in viral replication. This slipperiness is likely to be a long-term problem, because like all other coronaviruses (CoVs) before it, its potential host range and pools in which new pockets of SARS-CoV-2 can evolve and spillover to humans are large and therapies are limited. The emergence of SARS-CoV-2 is not special. It is an inevitability of modern human ecology and viral adaptation. The dominance of SARS-CoV-2 is special. Its circulation is likely permanent. Given this, what does it mean to control SARS-CoV-2?

The COVID-19 pandemic is extraordinary, but many ordinary factors contributed to its advent. All emerging human pathogens are the outcome of a complex combination of evolutionary, biological, and social factors. As such, pandemic mitigation requires an interdisciplinary understanding that is inherent to anthropology and to biological anthropology in particular. Here, we synthesize a history of SARS-CoV-2 from a biological anthropological perspective, addressing mitigation from the perspective of the virus's ecology, epidemiology, evolution, interaction with social factors, and place in disease history. We illustrate that this virus, which has radically altered day-to-day life for billions of people, is an inevitability of our contemporary human ecology, presaged by spillovers past (Lau et al. 2015). We discuss the circumstances of SARS-CoV-2 emergence and uneven disease burden while highlighting the exceptional features of the virus, COVID-19, and the formidable long-term ramifications of this pandemic for human health and well-being. We show the ways in which the history of SARS-CoV-2 thus far reiterates patterns of habitat encroachment, animal use, spillover, death, and disability common to multiple human pathogen pandemics in the recent past. Within that context, we conclude by describing features of SARS-CoV-2 and the COVID-19 pandemic that present opportunities for disease control: spaces for intervention in infection and recovery. From the perspective of "there are no more 'before times'," we encourage embracing a new future using old tactics, where mitigation is ongoing, public, reflexive, and supported.

CORONAVIRUSES PRE-2002: FASCINATING, ECONOMICALLY DAMAGING, BUT A NUISANCE

CoVs are a prolific viral subfamily of enveloped positive-strand RNA viruses (subfamily *Coronavirinae*, family *Coronaviridae*, order Nidovirales). They are so-called because under scanning electron microscopy a transmembrane protein essential for cellular entry known as Spike decorates the viral envelope, giving the virions the appearance of wearing a crown (corona) (Masters 2006). Strikingly, CoVs maintain the largest genomes of any RNA virus, with SARS-CoV-2 weighing in at an enormous (for viruses) 29,900 nucleotides. For these interesting features, most of what is known about CoVs has been discovered in the past two decades, after the emergence of severe acute respiratory syndrome (SARS) caused by the SARS coronavirus (SARS-CoV) in 2002 (Lu et al. 2020).

The first human CoV, recovered from embryonic tracheal organ cells taken from an adult with a cold, was discovered in the mid-1960s and, in a move unthinkable today, was later demonstrated to cause a common cold when it was deliberately applied to the noses of human volunteers (Kahn & McIntosh 2005). Shortly thereafter the strain (B814) was found to be structurally similar to two other newly discovered human viruses, as well as to multiple viruses isolated from chickens, mice, and swine. Rapid identification of CoVs across many mammals and birds ensued (Kahn & McIntosh 2005). These viruses are now attributed to the four genera of the subfamily *Coronavirinae*, *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. While a porcine *Deltacoronavirus* has recently been found to infect humans, viruses of the *Gammacoronavirus* and *Deltacoronavirus* genera are thus far known to infect primarily birds and ungulates and can generate substantial economic loss in the poultry and porcine industries (for reviews, see Ambepitiya Wickramasinghe et al. 2015, Lednicky et al. 2021, Wang et al. 2019). As of this writing all known circulating human CoVs belong to the *Alphacoronavirus* and *Betacoronavirus* genera, which find hosts in various mammals, including rodents, primates, carnivores, bovids, and cervids. Before SARS, however, human CoVs were thought to be a subset of viruses that cause only common colds—economically damaging, but largely a nuisance from a public health standpoint.

SMALL THINGS CAN RADICALLY CHANGE THE WORLD

The 2002 SARS outbreak infected approximately 8,000 people, killing 749 people across 29 countries, and radically changed the perception of human CoVs (Cui et al. 2019, Fehr & Perlman 2015). CoV research intensified. We now know that viruses from any of the four coronavirus genera can cause pathologies ranging from mild respiratory infections to severe pneumonia, encephalitis, gastroenteritis, and hepatitis in their hosts and that several viruses, including SARS-CoV-2 and strains of murine hepatitis virus, are capable of widespread tissue damage such as triggering the removal of myelin sheath from muscle (demyelination) (Fehr & Perlman 2015). Alphacoronaviruses HCoV-NL63 and HCoV-229E and betacoronaviruses HCoV-HKU1 and HCoV-OC43 routinely circulate in the human population and tend to manifest as mild respiratory and gastrointestinal infections in healthy people. Betacoronaviruses SARS-CoV (extant 2002–2004), Middle Eastern respiratory syndrome coronavirus (MERS-CoV) (extant 2011–present), and SARS-CoV-2 (extant 2019–present), which as of this writing (May 20, 2022) has infected at least 520,000,000 and killed over 6 million people, disrupted world economies and supply chains, and may have even precipitated war, can manifest as severe pneumonias and systemic infections (Dong et al. 2020). Since 2003, four more CoVs have been discovered in humans, and hundreds more in other animals, mainly bats (order Chiroptera) (Kahn & McIntosh 2005). All seven known human CoVs are thought to be the outcome of zoonotic transmission events to humans, mostly via bats (Cui et al. 2019, Rambaut et al. 2020) (see **Figure 1**). How does a small particle living in a small flying mammal come to exploit humans on a scale as grand as the COVID-19 pandemic?

SPILLOVER AND SPILLOVER, AGAIN AND AGAIN

Spillover describes the novel transmission of an infectious pathogen from one species to another. Zoonotic spillover to and from humans is affected by many factors, including human cultural practices (e.g., hunting, rearing livestock, irrigating dry regions), population characteristics that affect transmission likelihood (e.g., size, density), sociopolitical and economic events (e.g., conflict, forced migration, food availability), and environment shifts (e.g., climate change). However, the likelihood of such an event is much higher wherever humans and nonhuman animals are in frequent contact. Food systems, for example, can provide near-continuous contact between naive (new) and natural (original) hosts of a pathogen. The increased proximity of humans to nonhuman animals via domestication, for example, has led to multiple spillovers. Genetic

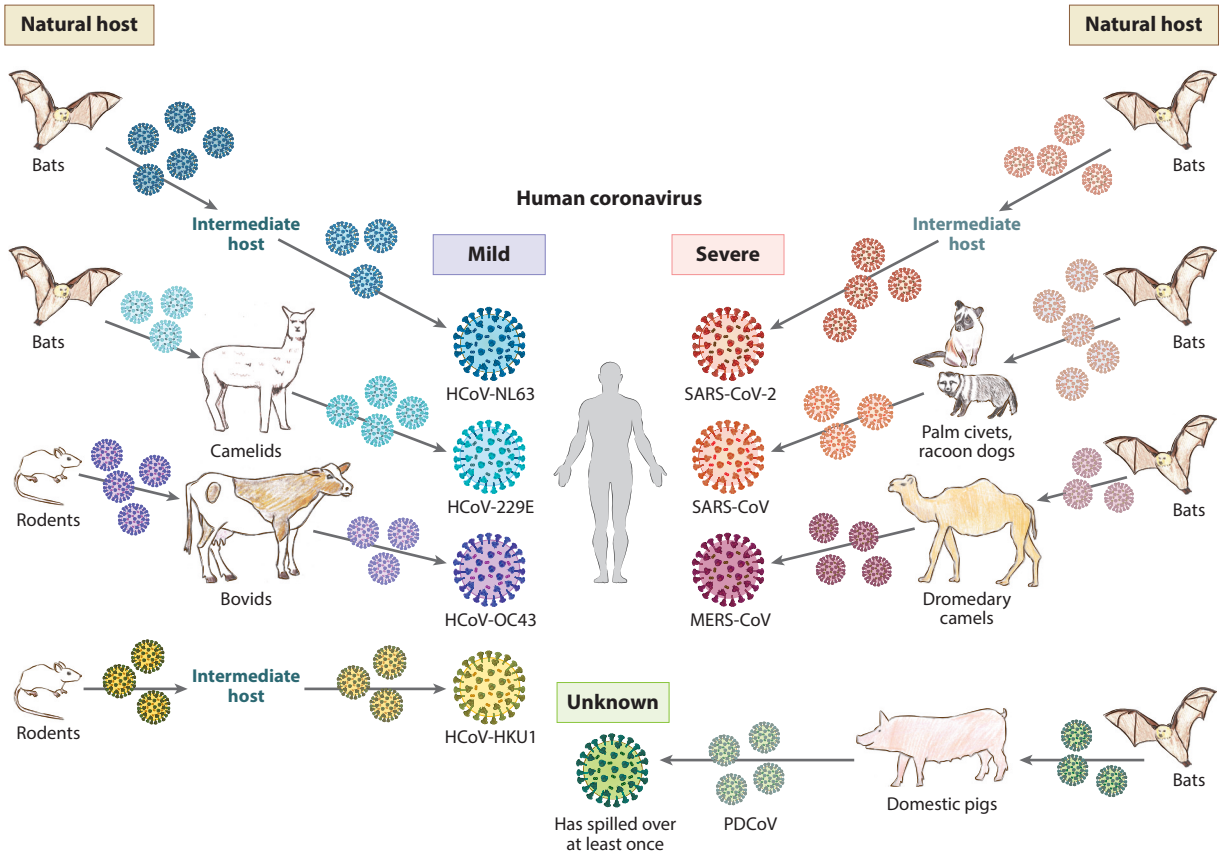


Figure 1

Extant, known human CoVs and recent spillovers. CoV spillover into the human population is frequent and repeated. All seven known human CoVs are the outcome of zoonotic spillovers from other mammals to humans. Recent evidence suggests that PDCoV, a member of the genus *Deltacoronavirus*, has spilled into humans multiple times recently via domestic pig operations. However, bats (order Chiroptera) play an outsized role in the hosting and proliferation of CoVs. A recent sampling of 20,000 animals representing 292 bat, primate, and rodent species finds that 91% of CoV-positive samples came from bats and that 98% of all bats sampled were positive for CoVs (Anthony et al. 2017). Several CoVs have passed from bats through an intermediate mammalian host (i.e., host species in the transmission chain from bats to humans, not to be confused with intermediate host in a parasite life cycle), usually domesticated or trafficked animals, before emerging in humans (Guan et al. 2003, Han et al. 2016). Thirty percent of all common colds in healthy people are caused by the alphacoronaviruses HCoV-NL63 and HCoV-229E and the betacoronaviruses HCoV-OC43 and HCoV-HKU1, which genomic evidence supports spilled over from bats via an unknown intermediate host, bats via camelids, rodents via bovids, and rodents via an unknown intermediate host, respectively. Betacoronaviruses SARS-CoV-2 and SARS-CoV, which are closely related genetically, share high genomic identity (i.e., identical genome sequences) with known bat SARS-related CoVs, a large group of viruses closely related to SARS-CoV with wide geographic spread, from Eurasia to Africa (Wu et al. 2020). SARS-CoV-2 shares ~96% genomic identity with the bat virus RaTG13, a SARS-related CoV sampled from the intermediate horseshoe bat (*Rhinolophus affinis*), strongly supporting the notion that the agent of COVID-19's origins is in a bat host (Zhou et al. 2020). Similarly, genomic and serological evidence suggests MERS-CoV is the descendant of a CoV transmitted from bats to domestic dromedary camels, circulating in the latter for at least 40 years before the first cases of MERS were noted in humans in 2011 (Han et al. 2016). Image created by authors and with BioRender.com. Abbreviations: CoV, coronavirus; MERS-CoV, Middle Eastern respiratory syndrome coronavirus; PDCoV, porcine deltacoronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

evidence suggests that human measles arose from the rinderpest virus that circulates in domestic sheep and cattle, and that the occurrence of all three human-infecting tapeworms (*Taenia* spp.) and the bacteria *Staphylococcus aureus* in cattle is the outcome of spillover from humans to cattle during domestication (Weinert et al. 2012; reviewed in Harper & Armelagos 2013). Moreover, one of the great clinical crises of our time, the meteoric rise of antimicrobial resistant bacteria that kill approximately 5 million people across the world annually, has been driven in part by our use of growth promoters and antibiotics in industrialized livestock operations and by our dissemination of the resulting animal products into the environment and household refrigerators over wide geographic areas (Antimicrobial Resistance Collaborators 2022, Manges et al. 2001).

The odds of zoonotic spillover also increase at the edges of ecosystems, where biodiversity tends to be high and species in the adjacent ecosystems are more likely to meet (Borremans et al. 2019). Over the past 50 years, spillover events between human and nonhuman animals have amplified and are increasingly common in part because over this period there have been global shifts in the human-driven environmental change at these edges, including industrial agricultural practices and climate change. Extractive industries, often driven by the appetites of high-income nations, have strongly contributed to increased spatial overlap between natural and naive hosts of pathogens capable of infecting humans (Alexander et al. 2018). Multiple Ebola (*Ebolavirus*) outbreaks over the past 40 years, for example, appear to have originated from human contact with infected animal carcasses at the edge of increasingly fragmented forested regions in West and Central Africa (Judson et al. 2016). As Benton & Dionne (2015) have noted, colonial history and continued practices, European or corporate, deeply influence dissemination after spillover or outbreaks of Ebola occur. In the past decade, Ebola outbreaks in the Democratic Republic of Congo, for example, have been made more severe not just by global economic marginalization but by conflict in the region directly interrupting patient isolation and vaccination programs (Borremans et al. 2019, Wells et al. 2019). These increasing and ongoing Ebola outbreaks in West and Central Africa reiterate another emergence. The rise, worldwide dissemination, and unequal burden of HIV have been driven by similar factors (see **Supplemental Text 1**).

Supplemental Material >

SARS-COV-2 SPILLOVER IS SPECIAL IN UNSPECIAL WAYS

Spillover events almost always fail to establish new host pools (Alexander et al. 2018). Pathogens that do spillover often share a set of circumstances and features. The reservoir host tends to be the target of human activities or broadly distributed in regions of human activity, and the pathogen is usually highly prevalent in that species. Human activities in the region often increase exposure to that pathogen (e.g., logging, hunting), the available dose of that pathogen via those activities tends to be high (e.g., tissues, blood during food preparation), and the pathogen is usually adapted to a transmission route to which the human activity provides access (e.g., blood-to-blood transfer, inhalation from tissue while preparing or eating) (Olival et al. 2017, Plowright et al. 2017). Infection of a naive host by a novel pathogen is not the only critical step in new pathogen emergence, however. There are many more spillover events than there are newly emerged pathogens because once in a naive host, the pathogen must be able to manipulate and escape host immunological factors and successfully navigate the host in a cell-by-cell order to replicate sufficiently to enable transmission from one naive host to the next (reviewed in Brinkworth & Alvarado 2020). For all the opportunity presented by transmission, host–pathogen match is critical to emergence. A microbe experiences little replicative success if, for example, the required receptors for cellular entry or manipulation are not available or there are immune factors in a host that can readily dispose of the invading pathogen. That SARS-CoV-2 spilled into our host pool and disseminated rapidly across the globe is special in this regard, except that it is not: These critical events happened multiple times before December 2019.

All SARS-CoV-2 genomes sequenced so far share novel mutations that were detected in samples acquired from patients in China in December 2019, suggesting a recent origin (Rambaut et al. 2020). Bat virus RaTG13 and SARS-CoV-2 diverge in sequence in the Spike protein receptor–binding domain that must bind to a human cell receptor for the virus to enter a cell. At the time of its discovery, SARS-CoV-2 had acquired mutations that improved its binding affinity to this receptor in humans [angiotensin converting enzyme 2 (ACE2)], but imperfectly. This imperfect binding suggests that spillover from bats to humans occurred not only recently but also after selection for improved binding, potentially via an intermediate host (Wan et al. 2020, Zhou et al. 2020). Analyses of all early SARS-CoV-2 genomes support a time to most recent common ancestor of October–December 2019. Approximately 70% of the first SARS-CoV-2 cases in China went no further than the first human host (Pekar et al. 2021, Rambaut et al. 2020, Roberts et al. 2021). In other words, those cases were self-limited and ended with viral strain die out. The COVID-19 pandemic, therefore, is the outcome of multiple spillovers. Since the earliest investigations into the outbreak it has been apparent that the SARS-CoV-2 circulating in the Hubei Province of China at the time of its discovery in December 2019 represents at least two distinct lineages of the virus: lineage B, found in the Huanan Seafood Market in Wuhan, China, and now throughout the rest of the world, and lineage A, recovered only from patients who visited other markets in Wuhan and other locations in China (Rambaut et al. 2020, Zhang et al. 2020). Together, these findings suggest that SARS-CoV-2 spilled over from a bat host into humans at least twice and that contact with the pathogen via its reservoir or an intermediate host prior to late fall 2019 was repeated.

If these events sound familiar, it is because bat-to-human pathogen spillover has happened many times. Bats maintain immunological and metabolic adaptations, potentially connected to powered flight, that seem to allow them to carry multiple highly pathogenic microorganisms without manifesting severe disease (see **Supplemental Text 2**). Humans have deeply encroached on bat habitats the world over via extractive industries such as mass agriculture, guano mining, and commercial bushmeat hunting, such that we not only eat bats but share, fragment, and overtake multiple resources of the order Chiroptera, including food and living spaces/roosting sites (Voight & Kingston 2015). The events leading to the emergence of SARS-CoV-2 approximate those that led to the emergence of SARS-CoV, MERS-CoV, three other human CoVs, and multiple agricultural CoVs over the past two decades. As with SARS-CoV-2, there is evidence of repeated spillovers for other SARS-related CoVs (SARS-rCoVs). Antibody surveys of people living in Yunnan Province, China, where SARS-rCoVs most closely related to SARS-CoV and SARS-CoV-2 have been found, determined that 3% of residents living near bat caves had been exposed to SARS-rCoVs (Wang et al. 2018). Investigations into the human SARS-CoV outbreak from 2002 to 2004, which was the outcome of spillover from bats to palm civets and raccoon dogs followed by spillover from these commonly trafficked animals to humans, found that more than 50% of traders trafficking civets had antibodies for SARS-CoV (CDC 2003). SARS-CoV-2 spillover also reiterates that of other viruses from bats, including mumps, Nipah, Hendra, and Ebola viruses (Anthony et al. 2017, Edson et al. 2015, He et al. 2020, Krüger et al. 2015, Leroy et al. 2009, Zhou et al. 2018). The proposed mechanisms of spillover for these pathogens include handling or mining of guano; catching spray from urine; handling animals that have recently been exposed to bat guano, urine, or flesh; eating bat resources (e.g., sap, fruit partially eaten by bats); and preparing bats for consumption (Akem & Pemunta 2020, Ayivor et al. 2017, Edson et al. 2015, Gurley et al. 2017, Wacharapluesadee et al. 2013). The emergence of SARS-CoV-2 is the outcome of the common human habit of environmental destruction, including the exploitation and disturbance of animals in bat habitats.

The exceptionalism of SARS-CoV-2 as an emerged human virus is, to a certain extent, based in its ordinariness. It is simply one of many pathogens that have spilled over from bats to humans,

Supplemental Material >

and repeatedly at that. It is a member of the most common emerging pathogen class: RNA viruses. Like other pathogens that have emerged before, SARS-CoV-2 is likely the by-product of habitat encroachment and animal use by humans. Like nearly 90% of human-infective RNA viruses, SARS-CoV-2 is zoonotic, with nonhuman animals serving as natural hosts (Woolhouse et al. 2013). Moreover, other CoVs have swept the human world multiple times in the past: HCoV-NL63, HCoV-HKU1, HCoV-229E, and HCoV-OC43 are globally distributed and cause approximately 30% of annual common cold cases (Cui et al. 2019). SARS-CoV-2 is not special. Its advent has long been considered a kind of inevitability, which is why CoVs and bats have been the focus of zoonoses monitoring and preemptive drug development and testing for the past two decades (Hu et al. 2017, Sheahan et al. 2017).

MAKE NO MISTAKE, SARS-COV-2 IS INDEED VERY SPECIAL

SARS-CoV-2, however, is special in its combined extraordinary transmissibility, virulence, and host range. The typical SARS-CoV patient transmitted the virus more than exponentially with a basic reproductive rate (R_0) of 2 to 4, meaning the average case, in the absence of mitigation measures, transmitted the virus to two to four other cases (WHO 2003). However, the case fatality rate of SARS-CoV was ~55%, and most people were symptomatic before they reached maximum ability to infect others (maximum infectivity) approximately a week later (Cai et al. 2006, Cevik et al. 2021, Donnelly et al. 2003). By contrast, SARS-CoV-2 infected 39,574,085 (with high estimates of approximately 146.6 million) people in the United States alone over roughly the same time period (February 2020–September 2021) and is much more transmissible than any of its predecessors (CDC 2021, Dong et al. 2020). The R_0 of the first global strains was more than exponential at 2.5–6.5 (Tang et al. 2020). The Omicron variant group (dominant at the time of writing) is maximally infective on the day of infection and has a relative R_0 calculated to be 4.2 times as high as the prior dominant variant (Delta), suggesting that each Omicron case, without mitigation, can give rise to a whopping ~10 other cases (Nishiura et al. 2021). This is "infection by walking into a recently vacated elevator" infectious. Indeed, a well-noted Omicron transmission occurred across the hallway of a quarantine hotel in China, the room doors of which were only briefly opened at different times for food delivery (Gu et al. 2022).

Very few pathogenic viruses exceed the basic R_0 of SARS-CoV-2 Omicron. The most infectious pathogen known, measles virus, has an R_0 of 10.5 to 18, infecting nearly every child in the United States prior to the advent of the measles vaccine (Glasser et al. 2016). Measles, even though it kills 1 in 1,000 infected individuals, is less deadly. SARS-CoV-2 from its emergence has demonstrated higher virulence, with 286.6 deaths per 100,000 in the United States so far (Dong et al. 2020, Glasser et al. 2016). That virulence is due in part to the virus's broad tissue tropism. Though SARS-CoV-2 enters a host through respiratory and alveolar epithelial cells, its main cellular targets are the endothelial cells of the circulatory system, meaning it disrupts hemodynamics (blood pressure) and can transit system-wide. The virus also enters the gut, central nervous system, placenta, eyes, heart, testes, liver, and kidneys in nonsevere infections and multiorgan involvement is typical of severe cases (Harrison et al. 2020, Hsu et al. 2021, Trypsteen et al. 2020).

Last, the potential host range of SARS-CoV-2 is exceptional. Mammalian vascular endothelium carries high levels of the SARS-CoV-2 mandatory receptor for cellular entry, ACE2. ACE2 is central to stabilizing blood pressure, and its conserved sequence in mammals likely explains the large known and potential host range of SARS-CoV-2. So far, more than 20 mammalian species have been confirmed as hosts of SARS-CoV-2 and can potentially serve as host pools from which competitive variants can spill back and forth to and from humans, creating a persistent threat to human health, animal conservation, and agricultural industries (**Figure 2**). These combined

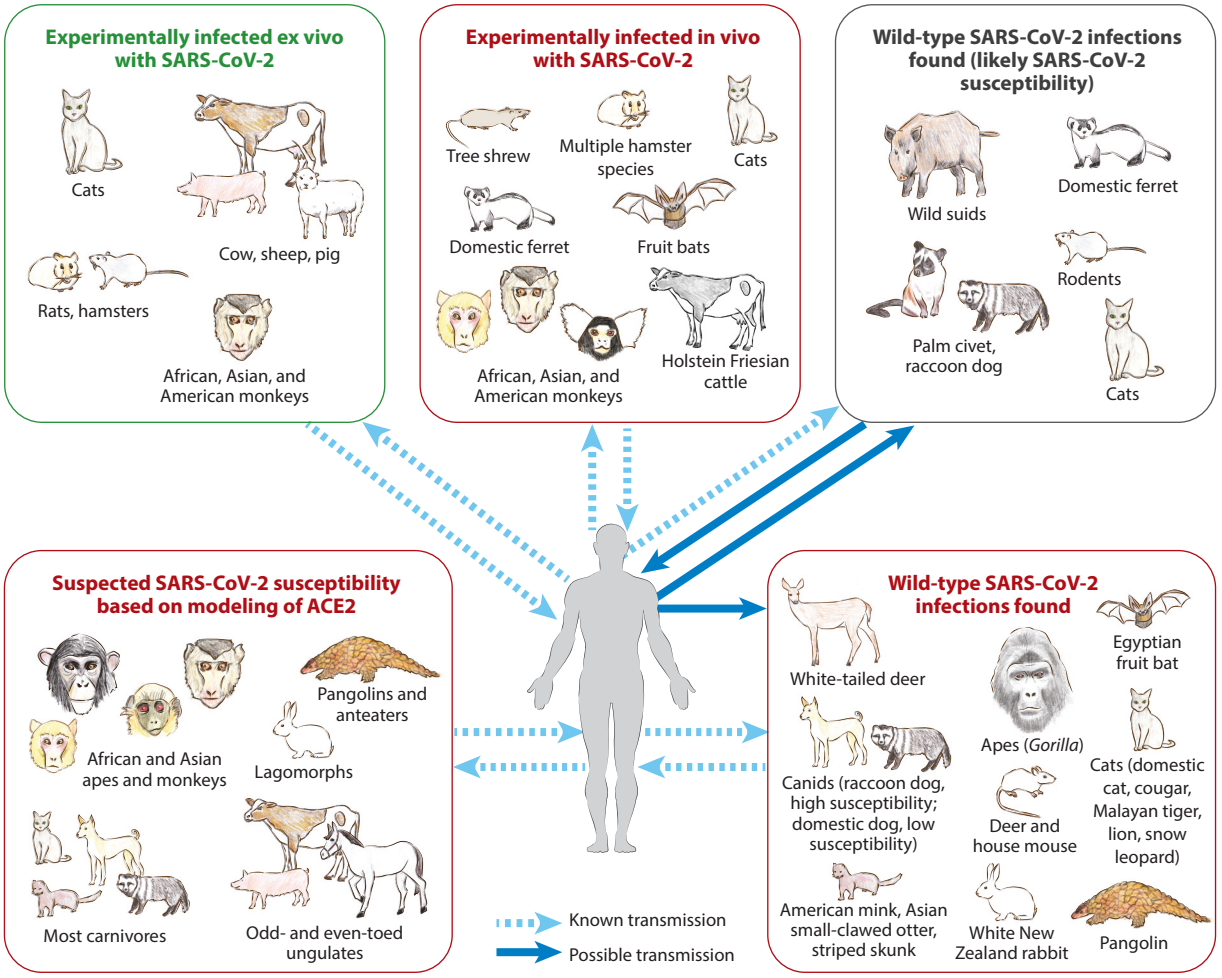


Figure 2

Known and suspected potential hosts of SARS-CoV-2. CoVs are exceptionally well adapted to spillover across mammalian and avian species. Cellular entry receptors are decisive in determining host range but differ across CoVs, and it is possible that not all entry receptors are known. Both SARS-CoV and SARS-CoV-2 use host ACE2 to enter host cells. However, even if the amino acid sequence of ACE2 is highly similar between susceptible and resistant species, it is not necessarily well expressed in tissues along human transmission routes (e.g., respiratory tract). For example, some swine have high ACE2 sequence identity with humans but low expression in the respiratory tract, which may explain why SARS-CoV-2 infections have been successful in swine cells ex vivo but not in some swine cells in vivo. Here, we show all animals known or suspected to manifest SARS-CoV-2 infection to date (March 10, 2022) that may serve as host pools for spillover and spill back to humans (Di Teodoro et al. 2021; Hobbs & Reid 2021; Meekins et al. 2020, 2021; Sreenivasan et al. 2021). Image created by authors and with BioRender.com. Abbreviations: ACE2, angiotensin converting enzyme 2; CoV, coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

characteristics make SARS-CoV-2 not only a more successful zoonotic virus than SARS-CoV but a greater threat to human health than most currently known circulating viruses.

IT IS A WIDESPREAD CAUSE OF DISABILITY

The long-term impacts of SARS-CoV-2 infection are tied to one of the four ways COVID-19 manifests as defined by the first reports of the illness: asymptomatic, mild (i.e., uncomplicated

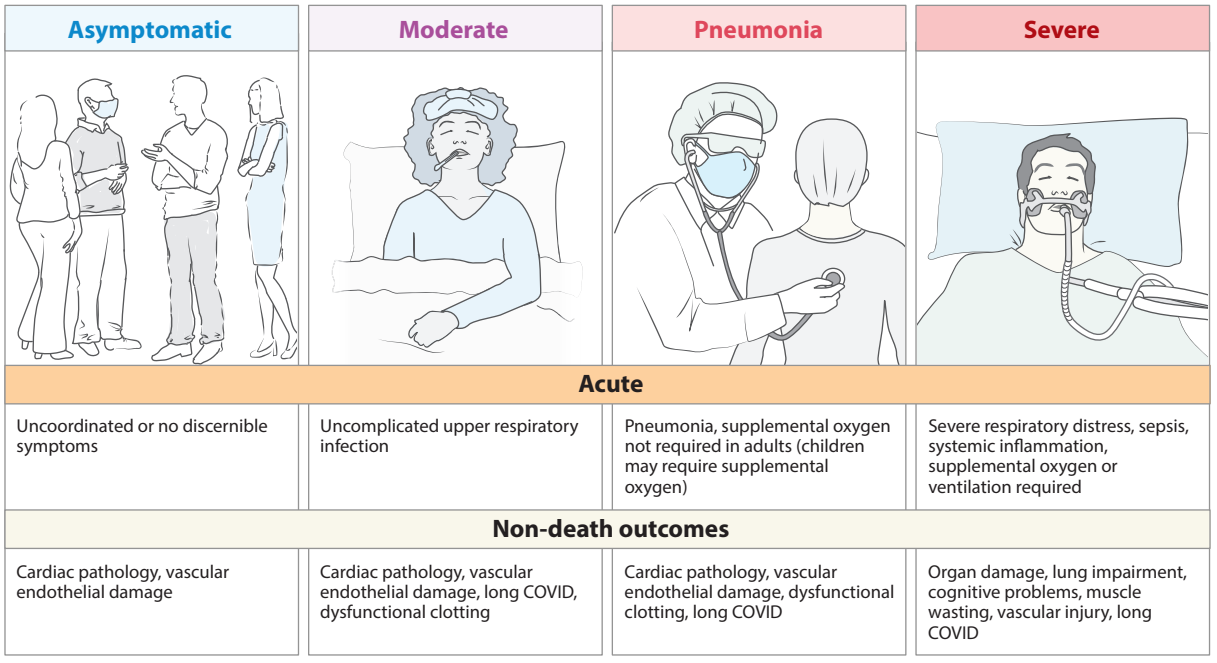


Figure 3

SARS-CoV-2 manifestations and associated non-death outcomes. SARS-CoV-2 is an agent of injury and disability. Non-death outcomes in severe cases include organ damage and lung impairment. Prior data on sepsis survival suggests older patients with severe COVID-19 will suffer postsepsis syndrome, 60% will go back to the hospital within the year, and 80% will die within 5 years (Annane & Sharshar 2015, Shankar-Hari & Rubenfeld 2016). Nearly 90% of COVID-19 survivors who were hospitalized with pneumonia suffer chronic conditions afterward, including kidney dysfunction, restrictive lung impairment, and pulmonary fibrosis (reviewed in Long et al. 2022, Salem et al. 2021). Mild infections most often trigger long COVID in young, healthy adults and children (Augustin et al. 2021, Borch et al. 2022, Erol et al. 2022). Long COVID can last more than 1 year in adults and approximately 5 months in children; it is characterized by extreme fatigue as well as persistent headaches, positional orthostatic tachycardia syndrome, sweating, muscle pain, cognitive dysfunction, and difficulty concentrating (Augustin et al. 2021, Borch et al. 2022, Boscolo-Rizzo et al. 2021, Erol et al. 2022, Ferrucci et al. 2021, Rai et al. 2022). Endothelial and cardiac damage, immune cell reprogramming in the bone marrow, neuroinvasion, and chronic infection (e.g., Epstein–Barr virus) are potentially responsible (De Felice et al. 2020, Gold et al. 2021b, Ryan et al. 2022, Sollini et al. 2021). Between 10% and 30% of COVID-19 patients report ongoing long COVID symptoms after the resolution of acute infection (Roth et al. 2021). Mapped to the current US case count, the range 10–30% suggests approximately 8–24 million cases in the United States have had or continue to experience long COVID as of May 20, 2022. Such a range represents approximately 10–30-fold the annual number of people who have heart attacks in the United States prior to the pandemic (Dong et al. 2020, Fryar et al. 2012). Asymptomatic infection is associated with cardiac pathology and vascular endothelial damage in young people (Umbrajkar et al. 2021). Both manifestations contribute to postinfection cardiac tissue damage, dysfunctional clotting, vasoconstriction and relaxation problems, edema, arrhythmias, and sudden cardiac death (Kim et al. 2021, Umbrajkar et al. 2021). Image created by authors. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

upper respiratory infection), mild pneumonia (adult pneumonia that does not require supplemental oxygen, though pediatric cases may need supplemental oxygen), and severe pneumonia (i.e., severe respiratory distress, sepsis) (Guan et al. 2020, Zhou et al. 2020) (**Figure 3**). In all cases, recovery can be steep. COVID-19 that progresses to severity (i.e., sepsis) deeply injures the host. Most patients who recover from sepsis and severe COVID-19 suffer a cluster of injuries and dysfunctions known as postsepsis syndrome, including persistent fatigue, lung fibrosis, kidney damage, executive function difficulties, immunosuppression, and muscle wasting, such that dressing and basic routines are challenging (Annane & Sharshar 2015, Puchner et al. 2021, Taquet et al. 2021). Older adults are not the only ones who struggle to recover. The 5% of infected

children who progress to severity face similar problems if they survive, including recovery from organ damage, muscle demyelination, brain swelling, and vascular injury (Cheung et al. 2020, Feldstein et al. 2020, Gulko et al. 2020, Sandoval et al. 2021).

Even when a person is fully vaccinated against severe COVID-19, SARS-CoV-2 infection can have long-term ramifications. Asymptomatic cases have been associated with cardiac pathology in young, healthy people, and vascular endothelial damage occurs in ~30–75% of all COVID-19 cases regardless of infection severity (Umbrajkar et al. 2021). Mild COVID-19 infections in adults and children are associated with an extended postviral syndrome, reminiscent but divergent from Epstein–Barr virus–mediated chronic fatigue known as long COVID (Augustin et al. 2021, Borch et al. 2022, Erol et al. 2022) (for more information see **Figure 3**). Almost 3 years into this pandemic it is clear that transmission of this virus matters on a much grander scale than severe infection because the virus can debilitate. Worse, the infection burden is uneven.

WHO GETS AND WHO DIES OF COVID-19 FOLLOW A PATTERN KNOWN AND LITTLE ALLEVIATED FOR DECADES

In the United States, who gets and who dies of SARS-CoV-2 follow a decades-known pattern of increased susceptibility to severe infectious disease. Like the leading infectious disease killers in the United States and worldwide (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*), the leading risk factor for severe SARS-CoV-2 is age (infancy or advanced age) (Martin et al. 2006, Novosad et al. 2016). Thereafter, the most common comorbidities (underlying conditions) for severe COVID-19 are clinically overlapping conditions that commonly co-occur and that are associated with either disrupted vascular endothelial function or altered lung and adipocyte inflammatory profiles, including obesity, hypertension, cancer, metabolic disorders (i.e., type 2 diabetes), and pulmonary disease (Guan et al. 2003, Novosad et al. 2016). The leading predictor for both these comorbidities and severe infection in the United States and worldwide is not host genetics, activity, or pathogen. It is low income (Galiatsatos et al. 2018, Rudd et al. 2020, Rush et al. 2018).

Low income is a symptom of social marginalization. In a watershed examination of racial health disparities, Williams & Collins (2001) drew connections between a broad range of social inequities that alter health on racial lines and the central feature of US urban planning—segregation (Popescu et al. 2018). In the years since, a robust literature has demonstrated that in colonial states (e.g., former European colonies such as the United States, Canada, and Australia) many non-White identities, and particularly Black, Indigenous, and Hispanic identities, are experienced as marginalization via residential and economic segregation, resulting in opportunity loss that drastically lowers current and future income and intergenerational wealth (Ali et al. 2018, Bailie et al. 2010, Benn Torres & Torres Colón 2015, Gracey & King 2009, Williams & Collins 2001). The spreading effects of such economic marginalization include lowered life expectancy via altered health and immune function in both the short and long term through direct interference (e.g., acute stress that alters infection dynamics, asthma control, and hypertension) and indirect interference (e.g., limited food options, restricted health care, poor housing quality, crowded living conditions, chronic stress) (Cohen et al. 1991, Davy 2016, Hughes et al. 2017, Kershaw et al. 2011, Ojard et al. 2015, See et al. 2017, Thames et al. 2019, Topfer & Spry 2019).

Chronic stress in particular leads to increased basal levels of inflammation, which contributes to aberrant infection responses, low-level tissue damage, and radical tissue remodeling that expediates comorbidity development (Vedhara et al. 1999, Wong et al. 2013). For example, fibroblasts (tissue-building cells) that repair minor vascular endothelial damage due to blood pumped throughout the body are stimulated by persistent low-level inflammation to invade arterial tissue, weakening arterial plaques and creating new ones, progressing cardiovascular disease (Fioranelli et al. 2018). Among chronically stressed people wound healing slows, infection rates increase, and

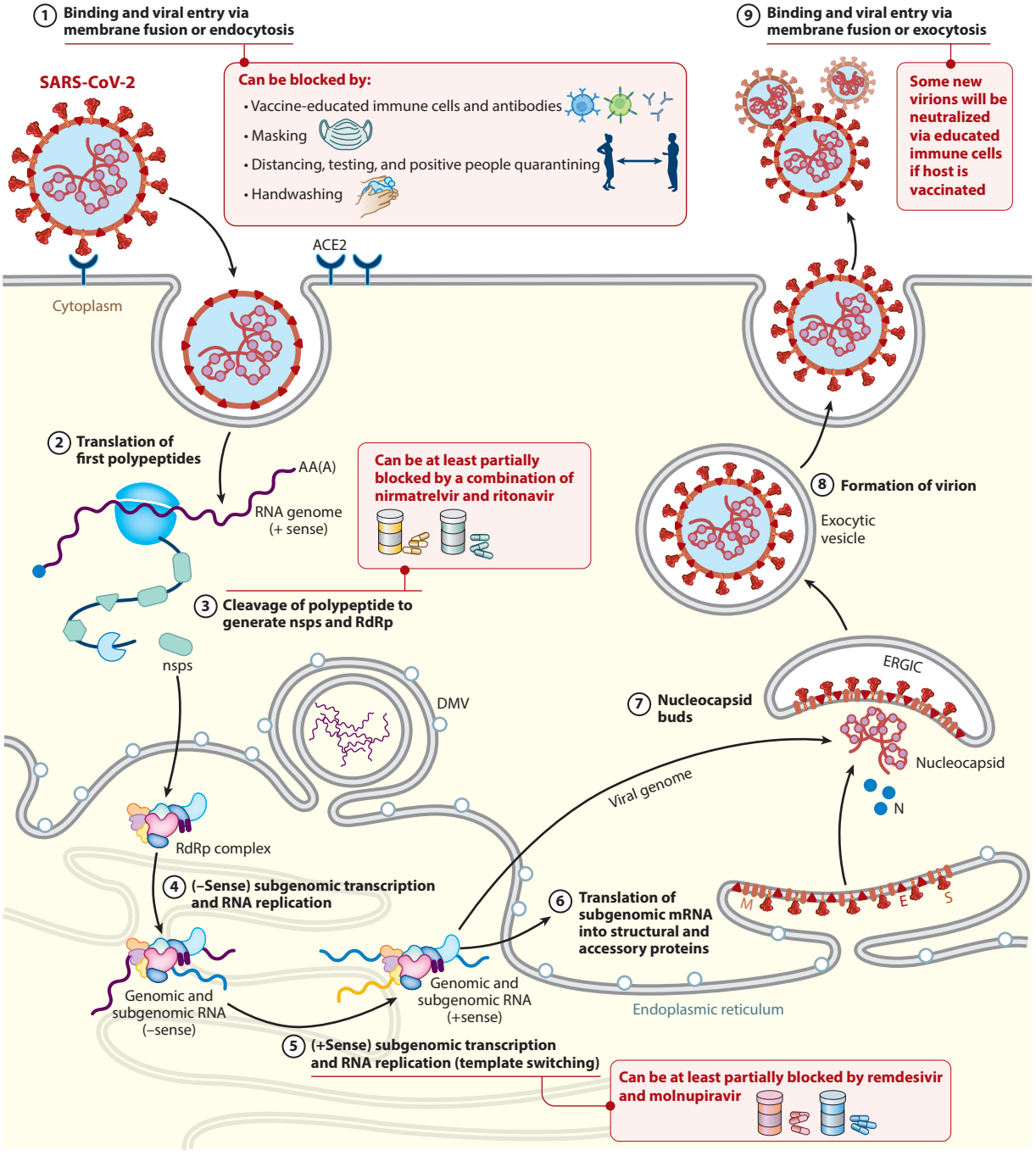
risk of severe infection comorbidities such as obesity, diabetes, and hypertension goes up (Cohen et al. 1991, de Heredia et al. 2012, Ebrecht et al. 2004, Fioranelli et al. 2018, Nicolaides et al. 2015). In the United States, Black, Indigenous, and non-White Hispanic people suffer greater economic marginalization, most frequently manifest severe infection/COVID-19 comorbidities, and disproportionately contract and die of COVID-19 (Brinkworth & Shaw 2022). On February 1, 2022, the age-adjusted risk of hospitalization with COVID-19 was approximately 2.5-fold higher for people identifying as Black or Hispanic and 3-fold higher for those identifying as American Indians/Alaskan Natives compared with Whites in the United States (CDC 2022). The risk of dying of COVID-19 is nearly double for non-White, non-Asian US peoples compared with White people. This is an age-worn pattern. Social marginalization is reflected in who gets and who dies of many other severe infections too, including sepsis (Barnato et al. 2008, Mayr et al. 2014, Rudd 2020). COVID-19 reiterates that the effect of marginalization over a lifetime so powerfully influences physiological function that it outstrips the impact of any one pathogen on severe infectious disease incidence or death (Brinkworth & Shaw 2022). As the late Paul Farmer (2020) emphasized, exoticizing a virulent pathogen belies the cold truth that poverty and denial of care amplify the pathogenesis of virulent infections.

If the suffering of others is not sufficient to redirect mitigation efforts of wealthy governments toward local and global health equity, that this suffering increases the likelihood of competitive viral variants should. Numerous highly virulent pathogens, including poliovirus, influenza A, and *Salmonella enterica*, shed longer, genetically drift, and increase in virulence in immunosuppressed people and animals (Dunn et al. 2015, Launay et al. 2021, van der Vries et al. 2013). While their hosts of origin are unknown and the variants monitored have arisen in wealthy nations, it is worth considering that four of the five SARS-CoV-2 variants of concern (Beta, Gamma, Delta, and Omicron groups) emerged or were amplified in regions of low- and middle-income countries (Brazil, India, and South Africa) that have high levels of poverty and untreated chronic infection (e.g., HIV-1) (Buss et al. 2021, Cherian et al. 2021, Viana et al. 2022). Inequities in wealth and health care access that lead to widespread immunosuppression can create circumstances where competitive SARS-CoV-2 variants can emerge at accelerated rates. Health inequities that lower infection prevention in one community are a problem for and should attract the aid of all communities.

THE FORMIDABILITY OF SARS-COV-2 AS A TARGET IS THOUSANDS TO BILLIONS OF YEARS IN THE MAKING

The challenge in controlling SARS-CoV-2 once someone is infected stems in part from the fact that CoVs are perhaps 10,000 years old but maintain many RNA virus adaptations that reach back perhaps billions of years (Koonin et al. 2015, Woo et al. 2012). SARS-CoV-2 is a formidable manipulator of host immunity, and its ability to evade host defenses is due at least in part to an ancient RNA virus strategy of frequent genomic recombination. The process is a driving force in the genomic variation of CoVs and contributes to changes in tissue tropism, the rise of new strains, and the ability to spill into new hosts (Fehr & Perlman 2015, Lau et al. 2015). Like all positive-strand RNA viruses, CoV genomes escape host immune detection by mimicking host RNA and manipulating host organelles into immune factor barriers (reviewed in Chen & Guo 2016, Knoops et al. 2008, Romero-Brey & Bartenschlager 2014) (see **Figure 4**).

Each of these tactics is ancient, is mandatory for SARS-CoV-2 replication, and has proven difficult to directly target in drug design. However, all CoVs use Spike protein to bind to a host receptor on the cell surface to initiate cellular entry. For SARS-CoV and SARS-CoV-2 that receptor is ACE2 (Simmons et al. 2004; reviewed in Heald-Sargent & Gallagher 2012, Yong et al. 2021) (**Figure 4**). Blocking virus–host membrane fusion is perhaps the most readily achieved mitigation procedure. Vaccination, which generates lymphocytes and antibodies that block and



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

The SARS-CoV-2 viral replication cycle and the limited therapies available to restrict it. SARS-CoV-2 replication cycle steps and the available therapies on the US market include (①) SARS-CoV-2 binds to host ACE2 and fuses to the cell membrane to infect the cell. Blocking virus–receptor binding (e.g., vaccines, masking) is currently the most effective approach to halting infection. (②) The virus fuses with a host cell membrane and empties its genome into the cell cytoplasm. The genome is recognized as host mRNA and is translated by host ribosomes. CoV genomes are encoded on the positive-sense strand and have evolved modifications (a 5′ cap structure) that give them the appearance of host mRNA—adaptations millions of years old that allow them to avoid immediately triggering host immune responses (reviewed in Chen & Guo 2016). (③) The first two translated proteins (polyproteins pp1a and pp1ab) must then be cleaved into 16 proteins required for viral replication and immune escape. Cleaved nsp1 shuts down the translation of host mRNAs, and a RTC is formed by the remaining cleaved proteins (Thoms et al. 2020; reviewed in V'Kovski et al. 2021). One of two antiviral drugs currently authorized for use in the United States, a combination therapy of nirmatrelvir and ritonavir, blocks the cleavage of these polyproteins and the subsequent cascade of events by enzyme inhibition (Pfizer 2021). (④ and ⑤) CoVs must replicate their genomes by generating negative-sense strands and retranscribe and assemble them as positive-strand genomes. This process, template switching, relies on an RdRp to complete and cross-check this task for mutations. The antiviral drug remdesivir specifically blocks template switching, and the therapy molnupiravir interferes with template switching by inducing mutations, rendering the new genomes nonfunctional (Beigel et al. 2020, Imran et al. 2021, Kabinger et al. 2021). None of these postinfection therapies wholly restrict viral replication, but they lead to fewer genomes shuttled into new virions. Even when a patient receives these treatments, SARS-CoV-2 will (⑥) complete virion assembly inside a virus-generated sequence of protective outpouchings of host endoplasmic reticulum and Golgi apparatus. These double-membrane vesicles (⑦, ⑧, and ⑨) hide immunostimulatory viral components during assembly, provide the viral envelope, and engage in exocytosis (Knoops et al. 2008, Romero-Brey & Bartenschlager 2014). Vaccine-stimulated antibodies may then restrict released virions. The remaining therapies on the US market reduce inflammation during severe infection or constitute antibody treatments with low efficacy against Omicron. Figure adapted from "Life Cycle of Coronavirus" by BioRender.com. Abbreviations: ACE2, angiotensin converting enzyme 2; CoV, coronavirus; E, envelope; M, membrane; mRNA, messenger RNA; nsp, nonstructural protein; RdRp, RNA-dependent RNA polymerase; RTC, replication-transcription complex; S, Spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

eliminate virus via detection of Spike protein, and behaviors (e.g., masking, distancing, handwashing) limit the number of available viruses in a host to infect cells. Blocking fusion is also critical to mitigation, because once the viral envelope has fused to a host cell membrane, a patient has only limited, partially effective therapeutic options for restricting COVID-19 infection. This is why the World Health Organization (WHO 2022) has recommended governments normalize COVID-19 mitigation efforts and focus on surveillance and behaviors aimed at preventing infection.

WHAT DOES PANDEMIC MITIGATION LOOK LIKE WHEN THE TARGET IS BILLIONS OF YEARS AHEAD OF YOU, IS EVERYWHERE, AFFECTS PEOPLE UNEVENLY, AND HAS AN ENORMOUS HOST POOL?

With an R_0 of 2.5–10 over its brief history, SARS-CoV-2 is not and has never been epidemiologically endemic because its levels are not sustained in the population without outside inputs. Rather, without mitigation, case numbers of SARS-CoV-2 increase exponentially. If we seek to control SARS-CoV-2 as a threat to health, we must control its transmission. Endemicity means suppressing the virus's R_0 to 1 or less. If that seems impossible, let us reassure you that we have done this before. We have, periodically, achieved R_0 of 1 or less with other highly transmissible, virulent pathogens via vaccination programs (e.g., smallpox, polio, measles). Moreover, SARS-CoV R_0 was suppressed to 1.1 without the benefit of vaccines (WHO 2003). In 2022 we have an elegant, extremely flexible, and easy-to-manufacture series of messenger RNA vaccines of extremely high efficacy. But mitigation to endemicity is real work. It is especially difficult with a new case load of nearly 50 million (global) and 1.7 million (United States) people per month (March 2022) (Dong et al. 2020). It means addressing some uncomfortable realities, including that there are no more "before times." Nearly 3 years in, we must accept that we are in a new future, and the epidemiological history of CoVs demonstrates that the following measures are essential to successful mitigation to endemicity.

Surveillance and Masking Must Be Consistent and Ongoing

Surveillance, contact tracing, and prevention behaviors, including masking, are critical to reducing SARS-CoV-2 case counts just as they were for SARS-CoV (WHO 2003, 2022). The SARS-CoV-2 surveillance recommendations by WHO have emphasized adjusting the public to regular COVID-19 testing of people, surveying agricultural and wild animals, and taking action to prevent transmission into probable animal host populations (WHO 2003, 2022). These recommendations helped eliminate SARS-CoV. SARS-CoV was at least as transmissible as the first strains of SARS-CoV-2 and was transmitted to agricultural and trafficked animals (Cui et al. 2019, WHO 2003). The largest SARS outbreak, in Beijing, China, was eliminated via a combination of initial social distancing and efficient central command issuance of health worker training, stockpiled personal protective equipment (PPE), community health monitoring, changes in hospital ventilation, fever clinics, strict quarantine and masking, and contact tracing (Pang et al. 2003). All COVID-19 vaccines on the US market are authorized or approved to prevent severe infection, not transmission, which means other mitigation methods must be instituted to reduce SARS-CoV-2 spread. A preponderance of evidence shows that two-way masking, even cloth masking by both infected people and uninfected people, slows COVID-19 transmission (Howard et al. 2021). However, the action given the most credit for quashing SAR-CoV in Beijing is the speed of contact tracing and issuance of quarantine orders, which took under an hour for a given case (Pang et al. 2003, WHO 2003). For these combined efforts to be instituted effectively across a nation requires culture change that emphasizes interdependence and cooperation. Importantly, intense and consistent federal support for mitigation is mandatory and the United States has never had that.

Prevention of Severe Infection Is Lifelong and Requires Inequities Be Alleviated

The comorbidities that put people at risk of severe infection are acquired over the course of a lifetime and are strongly influenced by social inequity (Brinkworth & Shaw 2022). To this end, COVID-19 mitigation requires consistent, lifelong government support for the US public in order to ensure access to care and to ameliorate income inequality and sickness-related income loss on a scale that has not been instituted before. This means admitting the impact of extant US health policies on the public, which includes a four-decade trend of lower life expectancy than peer nations with universal care and decades of increasing income and health inequality, before directly addressing these issues via federal reform (Woolhandler et al. 2021). With the growing epidemic of long COVID and the additional burden COVID-19 illness puts on caregivers, federal support and policies for social and equitable health care, global vaccine and antiviral therapeutic access, and flexible leave policies are becoming more urgent (Power 2020, Roth et al. 2021). If this seems like a complicated "heavy lift" in the US labor and health care systems, consider that the US federal COVID-19 policy instituted in March 2022 substantially lessened COVID-19 surveillance compared with January 2022 (NCIRD 2022).

Federal Support and Accurate Case Counts Are Critical

Federal support and regional centralization of COVID-19 restriction efforts follow the lessons learned after the SARS-CoV pandemic and have typified the actions of wealthy nations with high vaccination rates and low case count numbers (Government of Canada 2021, Lu et al. 2021, WHO 2003). However, in the United States, which has had the highest matriculated case and mortality counts in the world at various times since February 2020, federal messaging and support around SARS-CoV-2 have been inconsistent across two federal administrations (Dong et al. 2020). Both the Trump and the Biden administrations inaccurately framed COVID-19 as a much

milder infection than it is when hospitalizations and case and death counts were breaking records (Liptak & Diamond 2021, Sullivan 2020). Both administrations rested their COVID-19 policies heavily on individual responsibility and vaccination (Tomori et al. 2022). As such, social distancing, quarantining, masking, and, importantly, the standards for counting COVID-19 cases have not been supported by unified federal standards and money and have been deeply inconsistent across the public (Kerr et al. 2021). This inconsistency has allowed for state-level pandemic mismanagement (Dincer & Gillanders 2021, Gold et al. 2021a). A recent state investigation, for example, has revealed that the Cuomo administration in New York State deliberately introduced case counting standards that underestimated COVID-19 case and death numbers in nursing homes by ~50% (Diaz & Nahimias 2022). In February 2022, the US Centers for Disease Control and Prevention dropped the recommendation of universal COVID-19 contact tracing. As such, the total COVID-19 case count of the United States has been continuously, deeply underestimated.

It is difficult to control a pathogen as transmissible as SARS-CoV-2 without an accurate case count. Reducing the virus's R_0 to 1 requires a layered approach of accurate public messaging on infection; a speedy alert system for infection contacts; easy-to-access, accurate, and reportable testing; comprehensive vaccine programs and mandates; and support for quarantine and masking (WHO 2022). Yet in March 2022 the US federal government dialed back support and issued COVID-19 guidelines organized around two insufficient principles: (*a*) a threshold of hospitalizations, which is a lagging indicator of infection and triggers a series of individual antirisk actions (e.g., wear a mask in public indoor settings), and (*b*) the end of mask mandates in most public spaces (NCIRD 2022). Under these actions and policies, risk of infection is relegated as an individual health concern, not a public health concern. In a scathing March 2022 commentary in *eClinicalMedicine*, Tomori and coauthors (2022) called the US federal government's characterization of COVID-19 as an individual responsibility "a moral failing." It can be argued the failure is grander than moral. To date, two US presidential administrations have achieved the lowest COVID-19 vaccination rate of any wealthy nation, and neither has consistently provided testing or PPE to the public or contended with underlying inequities that contribute to the unequal impact of SARS-CoV-2.

CONCLUSION

If our aim is to reduce SARS-CoV-2 to endemicity, governments must continue to engage in lessons learned from SARS-CoV and remain flexible when facing the new challenges that SARS-CoV-2 brings. Pandemic mitigation requires an interdisciplinary understanding of both pathogen and hosts and a reflexive approach to changes in either. A biological anthropological point of view, described here and which integrates knowledge of how human ecology and economies contribute to pathogen emergence/re-emergence, how host–pathogen interactions shape their coevolution, and how a combination of viral, social, and human behavioral factors influence disease epidemiology and unequal burden of disease, is necessary for mitigation of COVID, its fall out, and the new diseases that follow. Most importantly, like our ancestors, we must be flexible, adaptable, and work cooperatively. Although SARS-CoV-2 is rather ordinary in many respects and has accelerated long-standing issues, it has delivered a new future. Mitigation efforts are best served by embracing that there will be new variants and hosts and that new and old behaviors will be required of us.

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