Annual Review of Ecology, Evolution, and Systematics

Ecological and Evolutionary Insights About Emerging Infectious Diseases from the COVID-19 Pandemic

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Annu. Rev. Ecol. Evol. Syst. 2023. 54:171–93

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

https://doi.org/10.1146/annurev-ecolsys-102320-101234

Keywords

respiratory infection, zoonotic disease, evolution of virulence, social behavior, disease control, spillover

Abstract

The coronavirus disease 2019 (COVID-19) pandemic challenged the workings of human society, but in doing so, it advanced our understanding of the ecology and evolution of infectious diseases. Fluctuating transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrated the highly dynamic nature of human social behavior, often without government intervention. Evolution of SARS-CoV-2 in the first two years following spillover resulted primarily in increased transmissibility, while in the third year, the globally dominant virus variants had all evolved substantial immune evasion. The combination of viral evolution and the buildup of host immunity through vaccination and infection greatly decreased the realized virulence of SARS-CoV-2 due to the age dependence of disease severity. The COVID-19 pandemic was exacerbated by presymptomatic, asymptomatic, and highly heterogeneous transmission, as well as highly variable disease severity and the broad host range of SARS-CoV-2. Insights and tools developed during the COVID-19 pandemic could provide a stronger scientific basis for preventing, mitigating, and controlling future pandemics.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, starting in late 2019 and extending into 2023, was the largest disruption to global society since World War II. It caused more deaths in its first three years [at least 6.8 million (Johns Hopkins Univ. 2023)] than any disease since the 1918 influenza pandemic, which killed an estimated 50 million people (Taubenberger & Morens 2006). While the spillover and emergence of pathogens in new host species has been a topic of great interest for decades (Taylor et al. 2001), the COVID-19 pandemic was studied in far greater detail than any previous disease emergence, with data, tools, and collaborations that were not previously available. The result has been an amazingly detailed record of infections, cases, hospitalizations, deaths, viral sequences and traits, nonpharmaceutical interventions, estimates of vaccine efficacy for many different vaccines and endpoints (e.g., symptomatic disease, hospitalization, death), and much more. All this has led to both a rich understanding of the factors influencing the COVID-19 pandemic and a deeper understanding of several fundamental concepts in the ecology and evolution of infectious diseases. In this review, I focus on five general topics for which the COVID-19 pandemic has provided rich and deep insights:

1. The dynamic nature of human social behavior
2. Changes in selection on pathogens during establishment in new species
3. Changes in the realized virulence of human pathogens during establishment
4. The pathogens that pose the highest risk to humans
5. The impacts of disease in humans on the surrounding ecosystem.

These topics cover only a small part of the vast literature on COVID-19. There are >350,000 published articles on COVID-19 and tens of thousands of unpublished preprints, reports, and other media as of June 1, 2023. Due to space limitations, I am able to cite only one or two studies on a given topic, when there are often dozens or hundreds of relevant studies.

Before discussing the five topics listed above, it is worth restating three key concepts in disease ecology that were well known before the COVID-19 pandemic and that influenced how the pandemic played out. First, transmission of all pathogens is highly heterogenous, with a fraction of individuals contributing disproportionately to transmission (Lloyd-Smith et al. 2005, Woolhouse et al. 1997). SARS-CoV-2 was no exception, with more than half of cases infecting no one and a few cases infecting many (Endo et al. 2020). Differences among individuals in transmission were due to differences in both inherent infectiousness and contact rates (He et al. 2020, Ke et al. 2022) and to the environmental conditions where contact occurred. For example, transmission clusters were much more common indoors in spaces with poor ventilation than outdoors (Leclerc et al. 2020). This heterogeneity resulted, as it does for many diseases, in highly variable outcomes (Lloyd-Smith et al. 2005). Initial introductions sometimes led to explosive outbreaks, and there was disproportionate infection in some subpopulations, ethnicities, and socioeconomic groups (Karmakar et al. 2021, Williamson et al. 2020). Second, controlling spread by using symptoms to identify infected people is ineffective when a substantial fraction of transmission occurs from infected people without symptoms (Fraser et al. 2004). Presymptomatic, and to a lesser extent, asymptomatic transmission, was a hallmark of SARS-CoV-2 (Ferretti et al. 2020, Madewell et al. 2020). This made symptom-based screening ineffective for controlling SARS-CoV-2, despite it being successfully used to eradicate SARS-CoV-1; the latter had little presymptomatic transmission (Fraser et al. 2004). Instead, control of SARS-CoV-2 usually required repeated restrictions on activities and businesses, which were highly disruptive for society (Flaxman et al. 2020). Testing whole populations at relatively frequent intervals (Larremore et al. 2021) was also

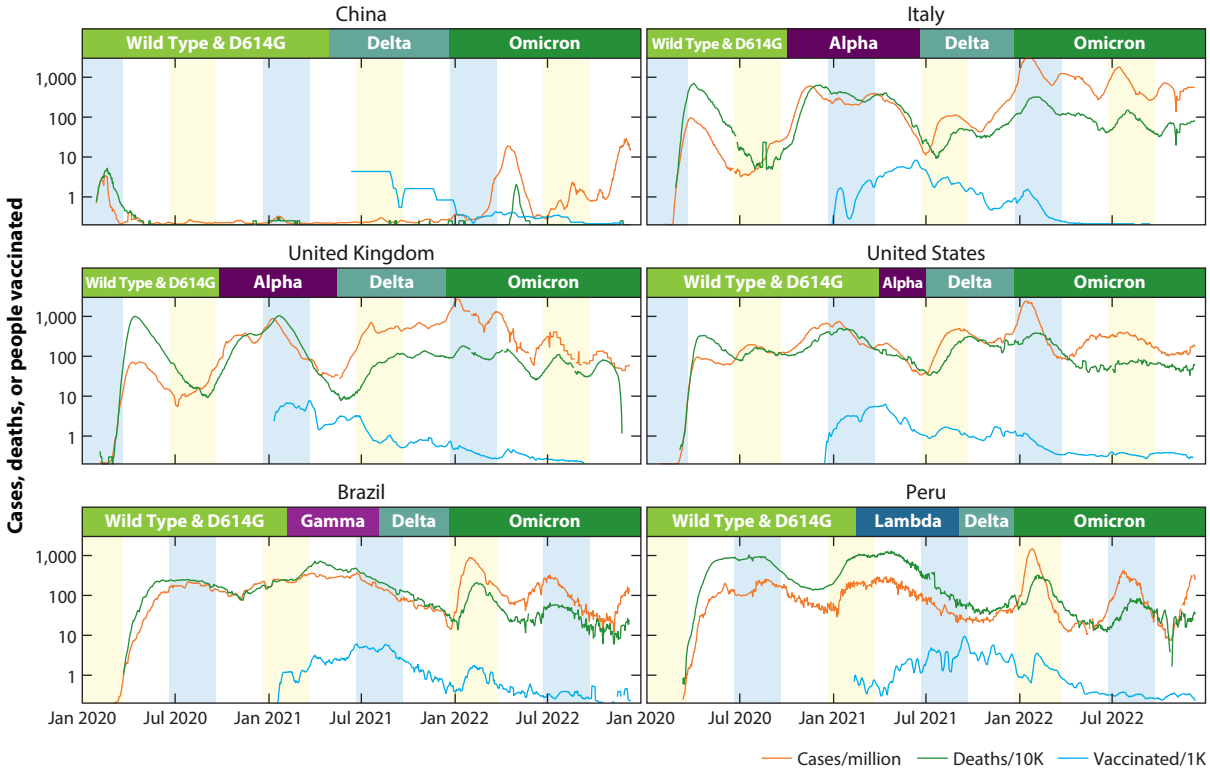

Figure 1

COVID-19 cases, deaths, and vaccinations (Our World in Data 2023) on a $\log_{10}$ scale and virus variants over time in six countries from January 1, 2020, through December 31, 2022. Rectangles across the top of each panel show the virus variant making up >50% of sequenced viruses in that country, based on 758K (Brazil), 7.7K (China), 607K (Italy), 174K (Peru), 4.5M (UK), and 5.2M (US) SARS-CoV-2 sequences from the Global Initiative on Sharing All Influenza Data (GISAID) (Shu & McCauley 2017). Blue shading shows winter periods, when established respiratory diseases are normally prevalent, and yellow shading shows summer, when they are usually less common.

used successfully by many organizations, and some whole countries (notably, China), to prevent ongoing transmission (**Figure 1**) (Rudan 2021). Third, the world is highly interconnected by air travel. Enacting travel bans against countries just after they have detected a new pathogen or virus variant is almost always too late to stop introductions, which will have already occurred. Travel bans are economically damaging and discourage surveillance and sharing information (The Lancet Infect. Dis. 2022). The futility of narrow, temporary, reactive travel bans was clear more than a decade ago during the H1N1 influenza pandemic (Hosseini et al. 2010) but was, nonetheless, repeated dozens of times by many countries over the first three years of the COVID-19 pandemic, with little success in stopping the introduction of the virus or virus variants (The Lancet Infect. Dis. 2022). Targeted travel restrictions may have temporarily slowed the rate of introductions, but only broad travel restrictions and aggressive local control were effective in keeping SARS-CoV-2 and its variants from circulating in local populations (Rudan 2021, Russell et al. 2021). Most countries did not implement broad travel restrictions, which led to rapid global spread of SARS-CoV-2 and, subsequently, spread of most variants to most countries. These fundamental concepts played a key role in how the COVID-19 pandemic unfolded.

As of May 2023, the COVID-19 pandemic had caused 6.9M reported deaths globally, with 1.1M in the US, and >200K reported deaths in six additional countries: Brazil, India, Russia, Mexico, Peru, and the UK (Johns Hopkins Univ. 2023); actual deaths in many countries were much higher (Karlinsky & Kobak 2021). The COVID-19 pandemic challenged the workings of human society. Human social behavior showed dynamic fluctuations, with populations substantially up- and downregulating contact rates, with, and sometimes without, government intervention. This led to surges in transmission in unexpected seasons and epidemics that stopped long before immunity became the dominant force arresting transmission. This is very different from the dynamics of most endemic diseases.

For many endemic human diseases, the seasonal dynamics are relatively stable. For example, in many temperate regions, most respiratory diseases, including influenza, the common cold, measles, and tuberculosis, have a clearly defined seasonality, with higher transmission often in cooler months (Martinez 2018, Moriyama et al. 2020). There is moderate year-to-year variation in transmission intensity and, in some cases, trends over time due to changes in public health, land use, climate, and other factors, but unseasonal transmission and large episodic outbreaks for these endemic pathogens are rare. For many diseases, this regular pattern is due to the fact that a large fraction of the population has been previously infected, and immunity limits both subsequent transmission and severe disease (Bjornstad et al. 2002). Seasonal transmission usually results from the combination of newly susceptible hosts (due to births, waning immunity, or viral evolution and environmental effects that increase pathogen survival outside the host), changes in host contact patterns (e.g., going to school), and/or changes in host immunity (Martinez 2018, Moriyama et al. 2020, Shaman et al. 2010). Previous immunity results in most established pathogens infecting a relatively small fraction of the population each year [e.g., influenza, 10–20% (CDC 2022a)].

In contrast, during the invasion of new pathogens like SARS-CoV-2, immunity initially plays a weak role, and this can provide unique insights into the relative importance of social behavior in disease dynamics. A brief timeline of the epidemiology of COVID-19 over the first three years in six countries serves to illustrate several key points (**Figure 1**). These six countries include five of the worst affected countries and China, with two countries in the southern hemisphere and four in the northern hemisphere (**Figure 1**), which allows us to examine the influence of seasonality and changes in social behavior on transmission.

SARS-CoV-2 originated in China in late 2019 (Pekar et al. 2021, 2022) and subsequently spread to neighboring countries and Europe in early 2020 and then throughout the US and globally (**Figure 1**). The virus spread rapidly as infections rose in China in late 2019, and by late January and early February, estimates suggest there were hundreds of imported infections per day into several European countries, which quickly grew to thousands of local infections in the next few weeks before airline flights from China were stopped (Nadeau et al. 2021). Although the full extent of the first surge in infections was poorly captured by case records due to limited testing capacity, COVID-19 deaths were more reliable, and I focus on these for inferring dynamics.

THE DYNAMIC NATURE OF HUMAN SOCIAL BEHAVIOR

The first surge in 2020 occurred during winter and early spring in the Northern Hemisphere and in summer and late fall in the Southern Hemisphere (**Figure 1**). Despite spreading in different seasons in the two hemispheres, spread was exceedingly rapid in both, demonstrating the larger importance of a naive population compared to seasonal variation in contact rates or pathogen survival, which elevates other respiratory infections in cooler seasons (**Figure 1**) (Baker et al. 2020). Epidemic trajectories were similar in Brazil and Peru in the Southern Hemisphere and Italy, the United Kingdom, and the United States in the Northern Hemisphere (**Figure 1**). The rapid rise

in cases and deaths led many governments to institute strict measures to reduce contact rates among individuals, including closing all nonessential businesses and services, making schooling remote, and encouraging at-home work whenever possible (Flaxman et al. 2020). Restrictions on human behavior were effective in many countries at reversing the initial growth in cases by April–May 2020, but not before large numbers of deaths occurred (**Figure 1**), and these interventions came at a huge economic and sociological cost (Flaxman et al. 2020, Hsiang et al. 2020). This put pressure on governments to lift restrictions as soon as possible, leading to a repeating cycle of surges, restrictions, and lifting restrictions that occurred several times throughout the pandemic (**Figure 1**). This repeating cycle of surges, restrictions, and lifting restrictions was, remarkably, anticipated by an early modeling study (Kissler et al. 2020).

Transmission of SARS-CoV-2 was stopped by changes in social behavior before a large fraction of the population had become immune. Estimates suggest that in most countries, less than 5% of the population was infected in the initial surge (O'Driscoll et al. 2021). However, when restrictions were eased in June–July 2020, transmission surged again in most populations at a time when respiratory infections are normally extremely rare in the Northern hemisphere (**Figure 1**, July–September 2020). This second surge subsided slightly during October and November 2020 in some countries, but in almost all countries [except those with strict borders and strong local control, including China, New Zealand, Australia, Vietnam, and a few others (Rudan 2021)], cases surged again in late 2020 as a more transmissible and more severe variant, Alpha (B.1.1.7), became dominant (**Figure 2**) (Volz et al. 2021). This third surge lasted through early 2021, until it was stopped by a new round of restrictions, just as initial doses of COVID-19 vaccines were becoming available.

Vaccines were distributed throughout 2021 in many countries (**Figure 1**, *blue lines*) and were critical in reducing deaths from a new virus variant, the more infectious and more severe Delta variant (B.1.617.2), which displaced the Alpha variant in the middle of 2021 (**Figures 1** and **2**) (Sonabend et al. 2021). Unfortunately, just as the Delta surge was slowing or waning in many countries due to vaccine- and infection-derived immunity, it was displaced by the highly immune evasive Omicron variant (B.1.1.529). The initial Omicron surge in early 2022 caused nearly an order of magnitude more cases than any previous surge (**Figure 1**), and this surge was followed by sustained transmission or fluctuations in cases every few months through 2022 as new subvariants of Omicron displaced the previous strain (**Figures 1** and **2**).

This abbreviated summary of the first three years of the epidemic illustrates the highly dynamic nature of human social behavior. Reductions in contact rates sometimes resulted from government restrictions: The initial epidemic in New York was avoided in California by preventative lockdowns (**Figure 3*a***). However, surges sometimes stopped without interventions, likely in response to surging hospitalizations and deaths that were widely covered by the media. For example, the summer surge in 2020 in the US subsided at a similar time in California, Texas, and Florida, despite restrictions being much weaker in the latter two states than in California (**Figure 3*a***).

The magnitude of the effect of fear-induced changes in behavior in today's media-saturated world was previously poorly known. This phenomenon had been previously examined theoretically (Funk et al. 2009), but detailed empirical studies have been limited primarily to nonrespiratory diseases that require less extensive behavioral change, with human immunodeficiency virus (HIV) being the best studied. Respiratory diseases had been studied only in a few smaller populations [e.g., SARS-CoV-1 in Singapore (Donnelly et al. 2003)]. The COVID-19 pandemic clearly demonstrated the potential impact of individual changes in behavior due to fear of disease.

The impact of behavioral changes can be illustrated by examining temporal variation in the pathogen reproduction number, R_t, over time (**Figure 3*b***). R_t describes the average number of

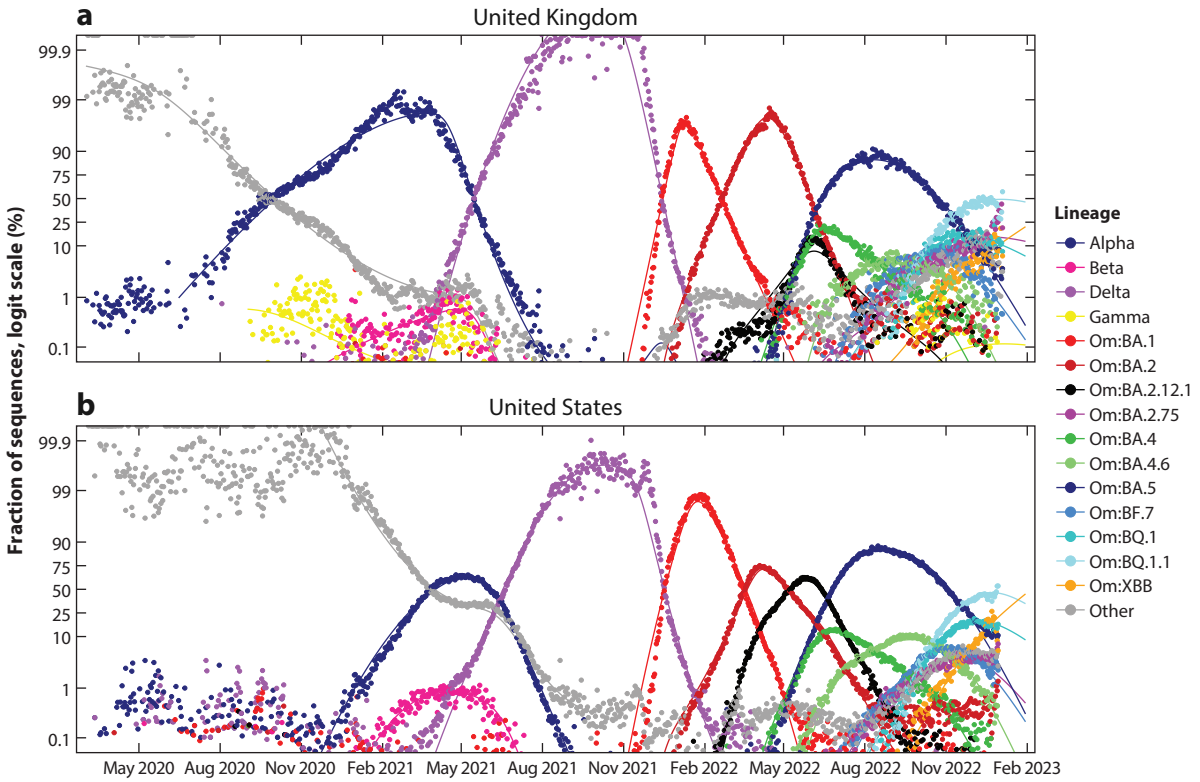

Figure 2

Fraction of (*a*) 4.5M sequences from the United Kingdom and (*b*) 5.2M sequences from the United States assigned to different variants from March 2020 to December 2022, based on data submitted to GISAID (Shu & McCauley 2017). Subvariants are shown for Omicron only. The gray line (Other) shows the fraction of predominantly early virus lineages (e.g., B.1), including those with the D614G mutation, until mid-2021. The lines show a fitted multinomial model. Abbreviations: GISAID, Global Initiative on Sharing All Influenza Data; Om, Omicron.

people that each infected person infects over their infectious life span. The time between one generation of cases and the next is termed the serial interval. Early estimates of R_t, before any public health measures were enacted, ranged from 2–5, indicating that the number of infections was approximately tripling every serial interval of 5–7 days (Flaxman et al. 2020, Gatto et al. 2020). In the absence of behavioral change, we would expect R_t to continuously decline in proportion to the rise in immunity and the fall in the fraction of the population that is susceptible, with relatively small deviations due to seasonal variation in transmission, like those observed for other respiratory pathogens (Martinez 2018, Moriyama et al. 2020). However, changes in behavior can lead to an increase in R_t over time, without a replenishment of susceptible individuals by birth or immigration. The repeated fluctuations in R_t for SARS-CoV-2 in many countries demonstrate the enormous shifts in social behavior observed during the pandemic. These fluctuations included large increases in unexpected seasons [e.g., summer 2020 in the US (**Figure 3*b***)] that did not coincide with the arrival of a new variant, as well as surges that ceased long before herd immunity was reached (O'Driscoll et al. 2021, Zhang et al. 2020). These changes in contact rate were also quantified with movement data based on cell phones, behavioral questionnaires, and restaurant visits (Del Fava et al. 2021, Dube et al. 2021, Nouvellet et al. 2021).

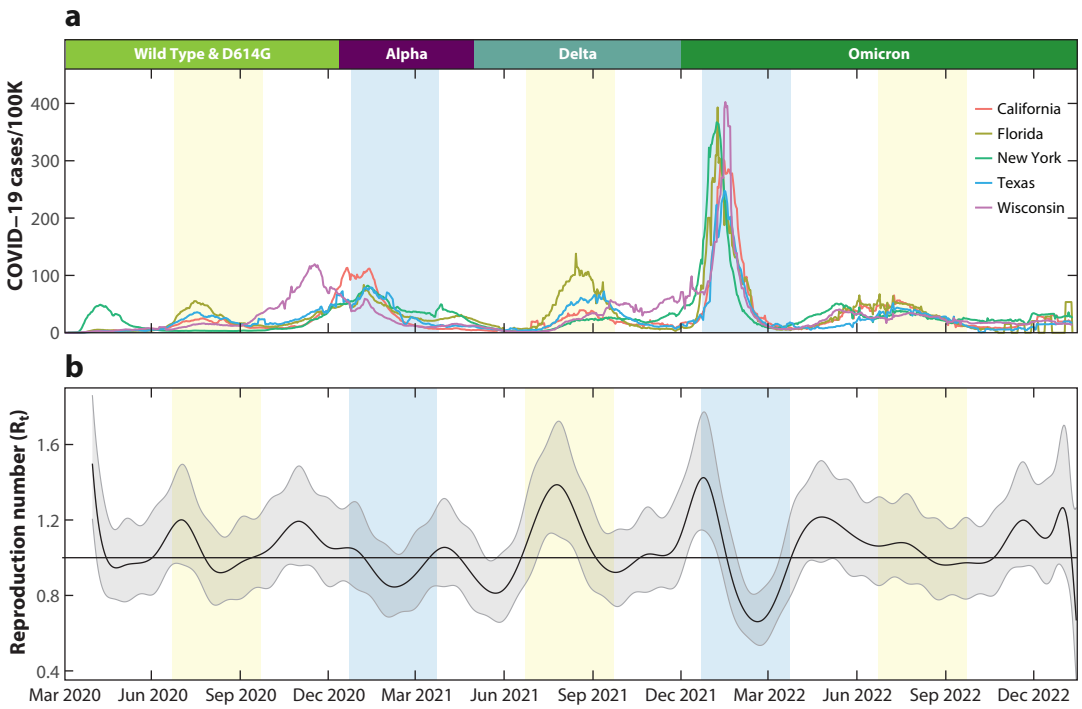

Figure 3

(*a*) Reported COVID-19 cases per 100,000 people in five states over the pandemic (data from the New York Times (2023). (*b*) The reproduction number, R_t, for SARS-CoV-2 in the US over the first three years (Shi & Gaynor 2023, Shi et al. 2022). Blue shading shows winter periods, when established respiratory diseases are normally prevalent, and yellow shading shows summer, when they are usually absent. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

CHANGES IN SELECTION ON PATHOGENS DURING ESTABLISHMENT IN NEW HOST SPECIES

The epidemiological summary above hints at another key insight gained during the COVID-19 pandemic: Selection pressure on the pathogen changed over time following spillover. The pandemic began with spillover of the virus from wildlife (likely bats) into human populations, possibly through an intermediate species, with two spillover events likely occurring in November 2019 (Pekar et al. 2021, 2022). Although the virus isolated in Wuhan was already moderately efficient at transmitting between people (R_t was between 2 and 5), it evolved substantially during the subsequent three years, with nearly 100 fixed single nucleotide mutations compared to the original virus, and several dozen reversions. The average number of substitutions was ~30/year, and a disproportionate number were in the spike protein, which the virus uses to enter cells and to which human antibodies bind (**Figure 4**) (Kistler et al. 2022, Nextstrain 2023). These changes in the virus occurred in pulses rather than gradually, with the emergence of novel variants that were quite different from earlier viruses. The four largest phenotypic changes in the virus were (*a*) a D614G mutation in the spike protein and three additional mutations in early 2020; (*b*) the emergence of the Alpha variant in late 2020, with 20 mutations compared to the predominant viruses circulating at the time; (*c*) the invasion of the Delta variant in mid-2021, with 13 mutations compared to Alpha; and (*d*) the evolution of the Omicron variant in late 2021, with 30 mutations in the spike protein and 20 others that had not been seen in combination before (**Figure 4**). The

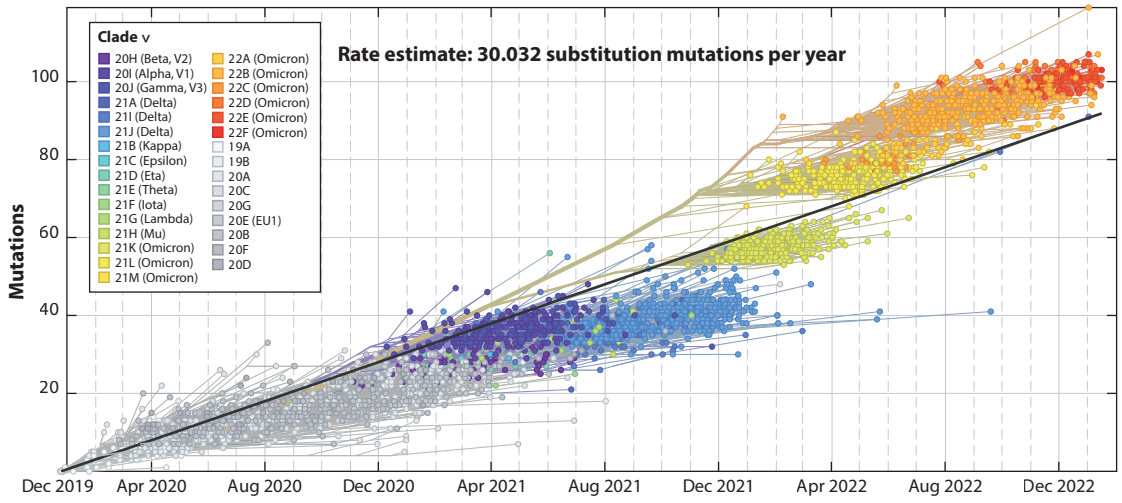

Figure 4

The number of substitutions between the ancestral strain (Wuhan-Hu-1/2019) and 3,102 sequences of SARS-CoV-2 subsampled from all available sequences on GISAID (Shu & McCauley 2017). Colors show the clade, using Nextstrain's nomenclature (Nextstrain 2023), with the WHO Greek virus variant name in parentheses. Clades in gray were circulating before the WHO developed the Greek letter naming scheme, beginning with Alpha. Abbreviations: GISAID, Global Initiative on Sharing All Influenza Data; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization. Figure reproduced from Nextstrain (2023) (CC BY 4.0).

mechanism(s) giving rise to new virus variants are not known, but hypotheses include evolution in chronically infected immune-compromised individuals; transmission of the virus to wildlife, followed by evolution and reinfection of humans; and evolution of the virus in poorly monitored populations (Choi et al. 2020). During 2022, sublineages of the Omicron variant acquired an additional 50 mutations with no sign of a slowing mutation rate (**Figure 4**). The phenotypic effects of mutations in the first two years primarily increased transmissibility; substantial immune evasion did not evolve until late 2021 by which time substantial immunity had accumulated through vaccination and infection.

The first mutations in SARS-CoV-2, including D614G and many of those in the Alpha, Gamma, and Delta variants, substantially increased the virus's transmissibility (Ives & Bozzuto 2021, Sonabend et al. 2021, Volz et al. 2021) and led to surges when cases were flat or declining (**Figures 1** and **3**). Selection for immune evasion was weak, because immunity was still limited in most populations before widespread vaccination in 2021 (O'Driscoll et al. 2021). However, by the end of 2021, most populations had substantial immunity, either from vaccination or from infection-derived immunity from Delta, Alpha, and other variants (**Figures 1** and **3**). This greatly increased the selective advantage for a variant that could evade acquired immunity, which Omicron did far better than any previous variant. Earlier variants that could evade acquired immunity did not have the same selective advantage globally (e.g., Beta) (**Figure 2**) because many populations had not yet acquired immunity, and none of these earlier variants had both immune evasion and higher transmissibility, relative to globally circulating strains (Althaus et al. 2021). As a result, early immune-evasive variants spread only in populations that had previously had large epidemics (e.g., Beta in South Africa) and never dominated global populations; they were eventually displaced by the more transmissible Delta variant (Giovanetti et al. 2022, Tegally et al. 2021). The selective landscape changed with vaccination and the accumulation of infection-derived immunity, which created a large advantage for immune evasive variants.

One way to examine phenotypic differences and quantify immune evasion of virus variants is to measure neutralizing antibody titers, i.e., to measure the concentration of antibodies in a person's blood and their ability to bind to, and neutralize, a virus (Smith et al. 1999). A key study showed that neutralizing antibody titers for a vaccine (or infection) against SARS-CoV-2 were strongly correlated with protection against symptomatic disease for different vaccines in randomized control trials (Khoury et al. 2021). This enabled the use of relative neutralizing antibody titer as a measure of immune evasion, and subsequent work validated this approach for the Omicron variant (Gardner & Kilpatrick 2021a).

There is sufficient data to examine immune evasion for three variants and three Omicron subvariants using relative neutralizing antibody titers. Relative to the original virus, neutralizing antibody titers were only ~1.5-fold lower for Alpha; ~2-fold lower for Delta, Lambda, and Gamma; and 6.7-fold lower for Beta. But, titers were 15–23-fold lower for Omicron, including 17-fold lower for BA.1, 15-fold lower for BA.2, and 23.4-fold lower for BA.4/5 (Gardner & Kilpatrick 2021a). The 2–3 fold differences in neutralizing antibody titer for the Alpha and Delta variants translate into relatively small differences in protection against infection and symptomatic disease [a 5–10% reduction from the original 90–95% effectiveness of vaccines and infection-based immunity against symptomatic disease (Gardner & Kilpatrick 2021a)] indicating that, while these viruses were more transmissible (Sonabend et al. 2021, Volz et al. 2021), they were not strongly immune evasive. In contrast, the 15–25-fold reductions in neutralizing antibody titers against the Omicron variant resulted in large decreases in protection compared to the Delta variant. Protection against symptomatic infection with Omicron was less than 20% for people with waned immunity (4–6 months after vaccination) (Andrews et al. 2022a,b; Gardner & Kilpatrick 2021b), which reflected most of the population in wealthy countries when Omicron spread to Europe and North America in late 2021 to early 2022. Omicron's ability to infect most people, despite previous infection or vaccination and including populations that were unwilling to comply with restrictions, resulted in an enormous global surge as the Omicron variant spread (**Figures 1** and **3**).

Viral evolution continued throughout 2022. Many new subvariants of Omicron emerged, with five subvariants reaching 50–90% in many countries before being displaced by another Omicron subvariant (**Figure 2**). Some subvariants have evolved slightly increased transmissibility, but the dominant feature of all Omicron subvariants has been immune evasion, i.e., an ability to infect individuals who were previously infected or vaccinated (Lyngse et al. 2022, Qu et al. 2023). Immune evasion by Omicron subvariants was facilitated by original antigenic sin (Aguilar-Bretones et al. 2023), in which reinfection leads to upregulation of antibodies that target the first virus variant a person was exposed to rather than developing new antibodies and T cells that target the new virus variant causing reinfection.

SARS-CoV-2 clearly evolved both increased transmissibility and, later, increased immune evasion. What about disease severity? Selection on disease severity for COVID-19 is mostly indirect, because severe disease occurs when people are only weakly infectious. Infectiousness wanes, on average, to a much lower level within 5 days of symptom onset (Ferretti et al. 2020), whereas severe disease occurs, on average, 8 days after symptom onset (Lewnard et al. 2020). Selection could alter disease severity either by increasing viral load, which would likely increase severity, or by altering the tissues it infects; infecting the respiratory tract rather than the lungs could decrease severity (Armando et al. 2022). Indirect selection and multiple pathways for evolution might explain why COVID-19 severity has changed in multiple directions over the first three years. Specifically, the Alpha variant caused more severe disease than the wild-type and D614G viruses and some studies suggest it led to higher viral loads (Davies et al. 2021). Delta also caused more severe disease and led to higher viral loads than Alpha (Twohig et al. 2022). In contrast, Omicron caused

less severe disease than Delta, likely due to less lung pathology, and was similar in severity to the original wild-type virus (Nyberg et al. 2022, Paredes et al. 2022). The fact that the virus evolved increased transmissibility that increased disease severity in two variants (Alpha and Delta) but decreased severity in Omicron suggests that selection on severity is not under strong direct selection. This means that future virus variants may be more or less virulent than currently circulating variants. Thankfully, the realized severity of disease in all but very young individuals in 2023 was much lower than in 2020 and will likely continue to decrease due to increased acquired immunity. COVID-19 will almost certainly never again be as deadly as it was in 2020.

CHANGES IN THE REALIZED VIRULENCE OF HUMAN PATHOGENS DURING ESTABLISHMENT

The COVID-19 pandemic has deepened our understanding of factors influencing disease severity. The virulence of many pathogens in animals, sometimes measured as the infection fatality ratio (IFR), or the chance of death following infection (Galvani 2003), has frequently been considered a relatively static property for a given pathogen variant. IFR often varies among ages, sexes, or nutritional statuses, but it is not generally considered a highly dynamic property that varies over time, unless there is a change in one of the population-level traits just mentioned or in the pathogen.

The COVID-19 pandemic demonstrated how the IFR can change dramatically over time. As SARS-CoV-2 invaded and became established, the accumulation of immunity from infection and vaccination, combined with viral evolution, led to a much lower likelihood of death, especially in older individuals. Before describing that pattern, however, it is worth noting that rigorously estimating the IFR is extremely difficult and has rarely been done, even for very important diseases (Riley et al. 2011). It requires quantifying all infections in a population, including both symptomatic and asymptomatic infections, and the number of deaths eventually resulting from those infections. Estimating the number of symptomatic and asymptomatic infections is difficult and usually requires a serosurvey, in which blood samples are taken and tested for antibodies that can be unambiguously linked to infection with that pathogen. Alternatively, if a population can be randomly sampled and frequently tested for infection and the likelihood of detecting an infection can be estimated, the total number of infections can be estimated (Riley et al. 2021).

Accurately estimating the IFR for a human pathogen is extremely rare, and rigorously quantifying it repeatedly in multiple populations, and over time, had never been done before the COVID-19 pandemic. This has limited our understanding of how IFR differs among populations and how it changes as a pathogen invades. However, during the first two years of the COVID-19 pandemic, the SARS-CoV-2 IFR was measured in multiple populations using serosurveys (O'Driscoll et al. 2021, Rickards & Kilpatrick 2023) and repeatedly over time using large-scale infection surveys (Eales et al. 2023). This produced a rich description of spatio-temporal variation in IFR during pathogen establishment that has previously been only the subject of speculation.

During the first wave of infection in 2020, before vaccines were available, IFR increased ~10,000-fold, log-linearly with age, increasing an average of 3.5-fold for every 10 years of age, from 0.001% in children 5–15 years old to 8.3% in individuals 80 and older (O'Driscoll et al. 2021), with some variation among populations in age-specific IFR related to income and income inequality (Rickards & Kilpatrick 2023) (**Figure 5**). The enormous increase in IFR with age resulted in most COVID-19 deaths occurring in older individuals, even when they were a relatively small fraction of the population (O'Driscoll et al. 2021).

Across entire populations, the initial IFRs in 2020 averaged nearly 1% among 45 countries examined (and varied between 0.1% and 1.1% depending on the demography of the country) (O'Driscoll et al. 2021). This population-level IFR puts COVID-19 approximately an order of magnitude above recent estimates for influenza (which shows a similar age–severity profile)

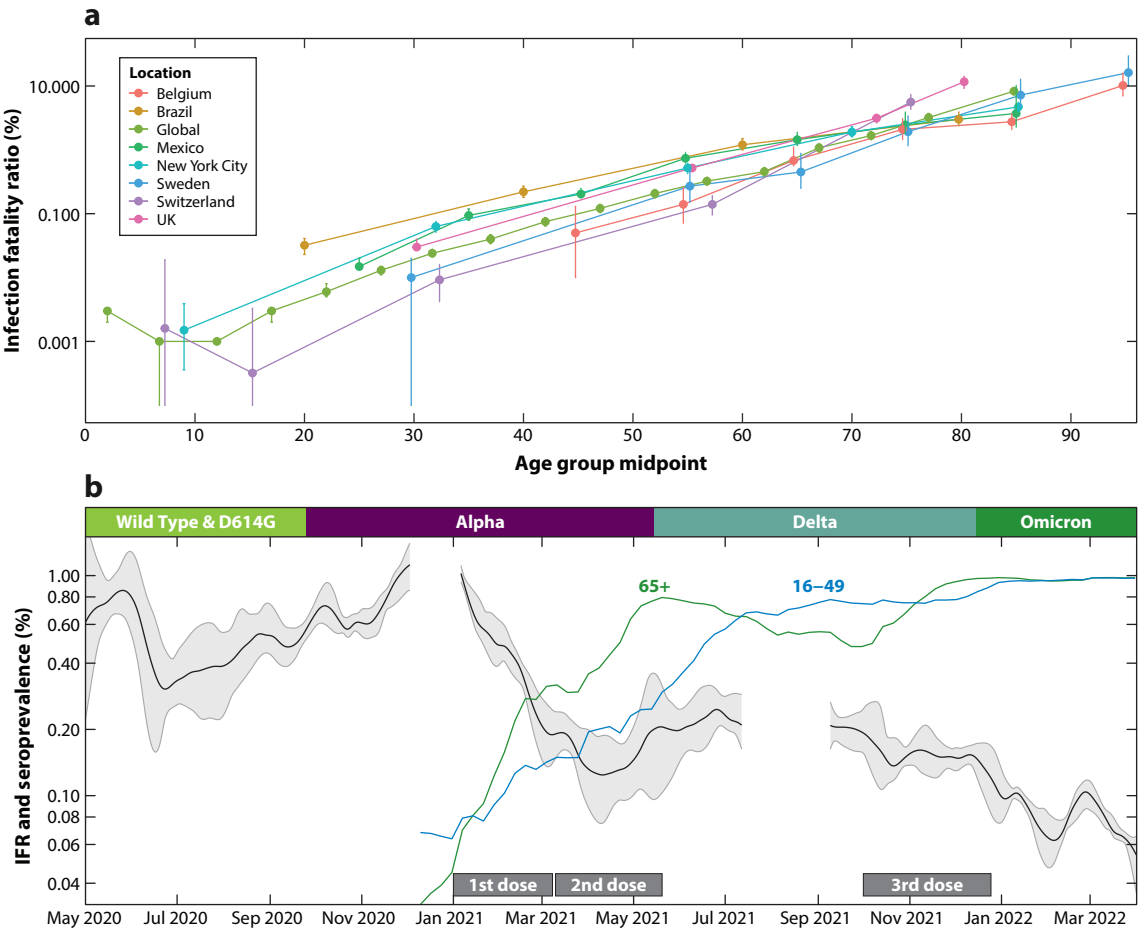

Figure 5

(*a*) IFR plotted against age for seven populations and a global estimate. (*b*) Population IFR, vaccinations, and dominant virus variant in England between May 2020 and March 2022. The black line and gray ribbon show the estimated IFR for all ages (deaths divided by infections 26, 26, and 18 days earlier for the three segments) and 95% confidence interval; the two gaps are periods with insufficient data to accurately estimate IFR. The gray bars along the bottom show the timing when approximately 90% of the first, second, and third vaccine doses were administered in individuals over 65 years of age, the age group in which most deaths occurred. The colored bars at the top of the figure show the virus variant that made up >50% of infections during that period; both variants were present for 0.5–1 month before and after the 50% threshold split. The green and blue lines show the fraction of the population with SARS-CoV-2 antibodies at the 179 ng/ml level or higher for individuals 65 years and older (*green line*) and 16–49 (*blue line*). Abbreviations: IFR, infection fatality ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Panel *a* created using data from Rickards & Kilpatrick (2023). Panel *b* created using data from Eales et al. (2023), except for the antibody seroprevalence data (UK Office for National Statistics 2023).

(Riley et al. 2011), and even farther above common cold viruses [which are a diverse group including rhinoviruses, other coronaviruses, parainfluenza viruses, and respiratory syncytial virus (RSV)] (Heikkinen & Järvinen 2003, Makela et al. 1998). Cold viruses are usually mild enough that too few deaths occur to accurately estimate the IFR. At the other end of the spectrum, the IFR of COVID-19 is certainly far lower than many other diseases including Nipah, rabies, SARS-CoV-1, and Ebola viruses, although no rigorous estimates of IFR exist for these pathogens (Aylward et al. 2014, Donnelly et al. 2003).

This broad comparison of disease severity among pathogens using the initial 2020 IFR for SARS-CoV-2 is seen from a different light if we examine temporal trends in the IFR of SARS-CoV-2 over the two years from mid-2020 to mid-2022 (**Figure 5*b***) (Eales et al. 2023). This analysis is based on an unparalleled data set collected in England, where 19 collections of swabs from at least 100,000 people each, selected at random, were tested for SARS-CoV-2 by RT-PCR approximately every month (Elliott et al. 2022, Riley et al. 2021). These data were used to estimate infection prevalence over time and were combined with data on reported deaths to estimate the IFR over nearly two years (Eales et al. 2023). This study (**Figure 5*b***) demonstrates three patterns in the population level IFR of SARS-CoV-2 over time: (*a*) The long-term trend is an enormous decrease, with the IFR at the end of March 2022 (∼0.06%) being tenfold lower than it was nearly two years earlier in May 2020 (∼0.7%); (*b*) there were at least two periods of sustained increase in IFR and three periods of sustained decrease; and (*c*) there were many additional sizeable short-term fluctuations over time. These three patterns reflect the combination of at least five factors, including: (*a*) different virus variants circulating in the population (**Figure 5*b***, *shaded*, *colored rectangles*); (*b*) the distribution of three doses of highly effective vaccines, especially to most older individuals (**Figure 5*b***, *gray rectangles*, *blue and green lines*); and (*c*) the accumulation of immunity acquired from infection, which boosted vaccine-derived immunity and provided immunity in unvaccinated individuals (**Figure 5*b***, *green and blue lines*); (*d*) changes in the ages of infected individuals; and (*e*) new treatments.

The timing and approximate contribution of these factors in altering the IFR in England is, as follows. The IFR decreased by more than half during June 2020 (**Figure 5**), likely due to a combination of new treatments and patient care (RECOVERY Collaborative Group 2021), reduced strain on hospitals, and possibly early death of the most at-risk individuals, often in skilled nursing facilities (O'Driscoll et al. 2021). The rise in IFR in late 2020 can be attributed to the invasion and eventual dominance of the more virulent Alpha variant and possibly increased stress on hospitals (Davies et al. 2021, Volz et al. 2021); the rise over the summer of 2020 is more difficult to explain. In contrast, the rapid, fivefold decline in IFR from ∼1% in January 2021 to <0.2% in April 2021 (**Figure 5**) is due almost entirely to vaccination of the population (**Figure 5**, *gray shaded vaccine rectangles*, *blue and green lines*); vaccine effectiveness against death was >96% (Haas et al. 2021, Meslé et al. 2021). This fall in IFR likely would have continued with increased vaccination coverage, but it was arrested and reversed by the invasion of the more virulent Delta variant (Sheikh et al. 2021, Twohig et al. 2022), which completely displaced Alpha (**Figure 2**). Deaths during the Delta surge were exacerbated by waning immunity and protection, especially in older individuals (**Figure 5**, *green line*). This led to a huge campaign to distribute third vaccine doses to ∼90% of the over 65 population between October and December 2021, which contributed to the IFR again declining in late 2021 (**Figure 5**). Finally, the IFR declined even further in early 2022 as the milder Omicron variant displaced the Delta variant (Nyberg et al. 2022). This rich and detailed description of temporal variation in the IFR was possible only through the herculean sampling effort to quantify infection prevalence over time (Eales et al. 2023, Riley et al. 2021), combined with independent studies of variant severity, vaccine effectiveness, and population-level immunity to provide the mechanisms underlying the patterns.

This combination of studies illustrates three general principles. First, while the realized IFR decreased tenfold over three years, this was not due to consistent viral evolution toward lower virulence. Variation in virulence attributable to the virus increased twice (Alpha, Delta variants) and decreased once (Omicron). This fits with our broader understanding of the variable directions of virulence evolution in animal diseases obtained from experimental infection studies (Fleming-Davies et al. 2018, Kerr et al. 2022). It is worth emphasizing that we have never before been able to precisely quantify IFR, or the factors influencing it, over time for a novel human disease. Second,

the IFR decreased enormously over the two years of the pandemic. This was due primarily to accumulation of immunity, which was most important in older individuals, in whom most COVID-19 mortality occurred (Eales et al. 2023, O'Driscoll et al. 2021). This accumulation of immunity and decrease in IFR would have occurred through infection if vaccines were not available, but with a much larger loss of life (Meslé et al. 2021). The third principle is that the age dependence of the IFR determines the extent to which the IFR declines as a pathogen invades and becomes established. If disease severity is highest for very young individuals, then IFR declines much less as a pathogen becomes established, because new births continually replenish susceptible individuals. In contrast, if disease severity increases substantially with age, as it does for SARS-CoV-2 (**Figure 5*a***), then the IFR falls quickly as immunity rises. Unless the pathogen evolves substantially increased virulence or near complete immune escape, the IFR never increases to its initial level. However, unvaccinated young children still experience the original severity of the virus variant when they are first infected. We are immensely fortunate that the severity of COVID-19 in young children is comparatively mild (**Figure 5*a***).

The dynamic pattern seen in the IFR of SARS-CoV-2 raises questions about the inherent virulence and magnitude of the age dependence of disease severity for established pathogens that would be observed if they occurred in a naïve population. For example, viruses that cause the common cold (including four human coronaviruses, HCoV-229E, -NL63, -OC43, and -HKU1) are considered very mild, with death rates so low in all but very old individuals that they are difficult to measure. However, it is possible that these viruses were, in fact, far more virulent, like SARS-CoV-2, especially in older individuals, when they first spilled over into human populations. High virulence in older individuals is rarely realized because few people reach older ages without being repeatedly infected with these viruses when young, which provides substantial protection against severe disease. Similarly, while we can quantify disease severity versus age for many established diseases (Glynn & Moss 2020), patterns for most diseases are shaped by acquired immunity from infection at younger ages. Only by tracking the disease severity of epidemics in totally naive populations (or at least naive individuals) can one accurately assess a pathogen's inherent virulence and the extent that it depends on age. For long-established diseases, examining severity in naive populations is extremely difficult because any population that is naive to globally circulating pathogens may differ in many additional ways that confound comparison. In summary, COVID-19 has provided insight into the virulence of pathogens that have spilled over in humans in the past. It has also offered key insights about which pathogens will be most dangerous for humans in the future.

THE PATHOGENS THAT POSE THE HIGHEST RISK TO HUMANS

Four characteristics of SARS-CoV-2 contributed to the severity of the COVID-19 pandemic: a wide host range (**Figure 6**), a large range in disease severity among people (**Figure 5*a***), substantial presymptomatic and asymptomatic transmission (He et al. 2020, Madewell et al. 2020), and highly heterogeneous transmission (Endo et al. 2020). These pathogen traits increased the severity of the COVID-19 pandemic and will likely contribute to future pandemics.

A key outstanding question is: Which wildlife pathogens are most likely to cause future emerging infectious diseases in humans? Two contradictory patterns have made it difficult to make a clear prediction. First, there is strong evidence that hosts that are more evolutionarily closely related are more likely to share pathogens (Gilbert & Webb 2007, Olival et al. 2017). This suggests that the most likely pathogens to spill over into humans come from great apes or other primates, as HIV-1 and HIV-2 did (Gao et al. 1999). However, a number of pathogens from distantly related mammalian groups and birds have spilled over into humans and caused substantial epidemics, including

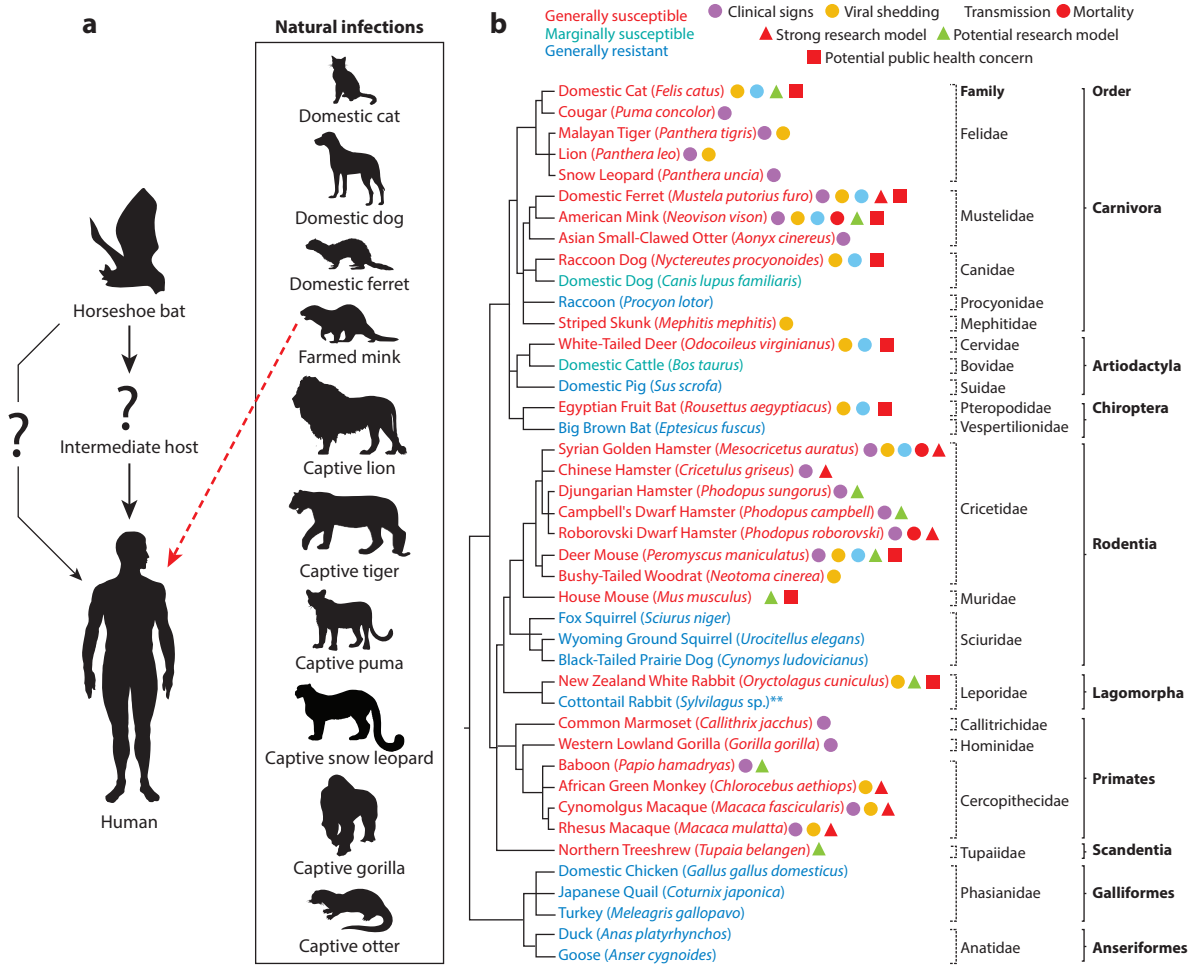

Figure 6

Host range of SARS-CoV-2 in domestic and wild animals. (*a*) SARS-CoV-2 likely originated in bats [possibly horseshoe bats (Holmes et al. 2021)], before spilling over into humans directly or via an intermediate host. (*b*) SARS-CoV-2 spilled back to many different animal species [and was transmitted back to humans from farmed mink (*red dashed arrow*)]; several additional species, spanning an enormous taxonomic range, exhibited clinical signs, including viral shedding, transmission, and mortality in experimental infection studies. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Figure adapted with permission from Meekins et al. (2021).

Ebola virus (Aylward et al. 2014), SARS-CoV-1 (Donnelly et al. 2003), and likely SARS-CoV-2 from bats (Holmes et al. 2021, Lytras et al. 2021); Lassa fever and plague from rodents (Luis et al. 2013); and influenza viruses from birds. While the wildlife reservoir for SARS-CoV-2 is not precisely known, most evidence supports bats being the source (Holmes et al. 2021, Meekins et al. 2021), and evidence suggests it was transmitted to humans from wildlife sold at the Huanan live market, where the first cases were concentrated (Worobey et al. 2022). Bats and rodents are also reservoirs for many other pathogens that are highly virulent in humans but have yet to cause large person-to-person outbreaks, such as Nipah virus from bats and hantaviruses from rodents. Recent work has shown that while taxonomically diverse mammalian orders such as bats and rodents do have more pathogens and more zoonotic pathogens than other orders, the risk of zoonotic

spillover per virus or per host species does not differ among mammalian orders (Mollentze & Streicker 2020). This begs the question: What traits of a pathogen make it likely to be able to infect humans, cause disease, and spread efficiently? One such trait is a wide host range. SARS-CoV-2 has demonstrated why.

SARS-CoV-2 has been shown to infect a wide taxonomic range of hosts including seven mammalian orders, with transmission or viral shedding occurring in six (**Figure 6*b***). Independent transmission cycles have been documented in farmed mink and wild deer (Hale et al. 2022, Lu et al. 2021), and a recent study of wildlife exposure based on detection of antibodies suggests widespread infection of additional taxa (Goldberg et al. 2022). Infection with SARS-CoV-2 also causes symptoms in six mammalian orders and many species (**Figure 6**). Taken together, these data clearly indicate that SARS-CoV-2 is a generalist pathogen.

What makes generalists pathogens so dangerous to humans? First, pathogens that can infect a wide range of hosts are more likely to be able to infect humans (Olival et al. 2017). There are few, if any, specialist pathogens of distant vertebrate taxa that can also infect humans. Instead, pathogens of bats, birds, rodents, and ungulates that infect humans all infect a wide range of hosts. For example, pathogens of bats that also infect humans include SARS-CoV-1, Middle East respiratory syndrome coronavirus, rabies, Ebola, and Nipah viruses. These pathogens all infect many other mammalian classes besides bats and humans (Chua et al. 2000, Li et al. 2005, Meekins et al. 2021, Olival et al. 2017). Similarly, zoonotic pathogens of birds, including West Nile virus and several subtypes of avian influenza (H5N1, H3N2, H1N1), infect and cause disease in a huge range of vertebrates (Kilpatrick 2011, Webster et al. 2006). Zoonotic pathogens of rodents, including plague, Lyme disease, and hantaviruses, are all also generalist pathogens (Luis et al. 2013).

Generalist pathogens pose multiple challenges for humans. First, there are multiple species that can transmit the pathogen to humans. Bats are recognized as the reservoirs for SARS-CoV-1, but evidence suggests this virus likely spilled over into humans via other distantly related mammal hosts, including civets and possibly raccoon dogs (Li et al. 2005). Similarly, Nipah virus can spill over directly from bats to humans (Epstein et al. 2020), but sometimes it is transmitted from bats to pigs to humans (Chua et al. 2000). The broad host range of SARS-CoV-2 may also have facilitated its spillover to humans.

Second, generalist pathogens are difficult to control because multiple species can act as reservoirs, which can prevent eradication of the pathogen from local areas. For example, SARS-CoV-2 is now widely established in deer populations in North America and possibly in other wildlife species (Goldberg et al. 2022, Hale et al. 2022). If SARS-CoV-1 had become established in wildlife on multiple continents, as SARS-CoV-2 has, eradication in humans may have been short lived and would have required renewed interventions following each spillover from wildlife.

The third challenge of generalist pathogens is that evolution of the pathogen in nonhuman hosts can result in novel mutations and combinations of mutations that might not be initially advantageous in humans but that could lead to dangerous new variants if the virus spills back over into humans (Rothenburg & Brennan 2020). Spillover and evolution of SARS-CoV-2 has been observed in white-tailed deer, farmed mink, and opossum (Goldberg et al. 2022, Hale et al. 2022, Lu et al. 2021), and may have occurred in other species. The processes that led to the emergence of new variants of SARS-CoV-2, including Alpha, Beta, Delta, and Omicron, which often have a large number of new mutations compared to circulating variants, is not fully understood. However, transmission to and evolution in wildlife and spillover back to humans is one hypothesized mechanism (Lu et al. 2021).

Given the frequent transmission of pathogens from humans to wildlife, the most prudent ways to avoid the challenges associated with generalist pathogens are: (*a*) to avoid initial spillover into humans by reducing human–wildlife contact; (*b*) to eradicate pathogens before they become

widespread in humans [as was done with SARS-CoV-1 (Donnelly et al. 2003)]; and (*c*) to reduce spillback to wildlife, again by limiting human–wildlife and domestic animal–wildlife contact. High rates of human–wildlife contact and shedding of SARS-CoV-2 into wastewater makes this very difficult and has resulted in extensive spillback of SARS-CoV-2 into many different species in many regions across the planet (Meekins et al. 2021).

Two additional characteristics of SARS-CoV-2 contributed to the severity of the COVID-19 pandemic and will worsen future pandemics: highly heterogenous transmission and highly variable disease severity. Heterogenous transmission makes it difficult to determine how the probability of transmission varies with the environment (e.g., temperature, humidity, and air flow) and more difficult to estimate the impact of different interventions including masks, distance, and hand washing (Chu et al. 2020). This uncertainty also hampers effective communication from public health officials who have to simultaneously explain why having more distance between people (e.g., 1–2 m or 6 ft), especially indoors, reduces risk (Chu et al. 2020) but that transmission between people separated by 4.6 m can still occur (Li et al. 2021). Similarly, even though many studies showed masks to be moderately effective (Chu et al. 2020), heterogeneity in transmission led to estimates of protection being highly uncertain with very wide confidence intervals [e.g., effectiveness for N95/KN95 masks is 83%, 95% CI = 36–95%; surgical masks 66%, 95% CI = 10–87%; and cloth masks 56%, 95% CI = 17%–83% (Andrejko et al. 2022)].

Highly variable disease severity also contributed to the COVID-19 pandemic in two ways. First, as described earlier, the risk of death given infection varied 10,000-fold with age (**Figure 5*a***). Within ages, the risk of death (not conditional on infection) also varied 2–3 fold for each of several preexisting conditions, including diabetes, kidney disease, and cancer (Williamson et al. 2020). This enormous variation in severity meant that many younger, healthier people assumed they would not suffer severe disease from COVID-19. Although young people's risk was indeed lower, it was not zero, and many healthy young people died. Less cautious behavior led to many more young people getting infected and then transmitting the virus to older people who died (Alwan et al. 2020).

The enormous variation in disease severity also made it much harder to refute false claims that infection was mild and not a real threat until enormous numbers of deaths had occurred (Alwan et al. 2020). For some other diseases, disease severity is less variable. For example, infection with Nipah virus almost always results in severe disease (Nikolay et al. 2019). If the next pathogen to spill over into humans and spread globally is both severe and less variable in severity than COVID-19, public health actions to reduce transmission and eradicate the pathogen from human populations may encounter less resistance.

In summary, the intermediate and highly variable disease severity of COVID-19, combined with highly heterogeneous transmission and presymptomatic and asymptomatic transmission, resulted in lower compliance with public health guidance and more resistance to interventions, which greatly increased the overall severity of the pandemic (Alwan et al. 2020, Flaxman et al. 2020, Meslé et al. 2021). Pathogens that share these characteristics are likely to cause substantial problems for humans in the future.

THE CASCADING IMPACTS OF COVID-19 IN HUMANS ON THE SURROUNDING ECOSYSTEM

The COVID-19 pandemic altered most human societies and had effects that rippled through ecosystems, including impacts on wildlife, on other pathogens of humans, and on global biogeochemical cycles. Most of these changes were temporary, but the pandemic allowed us to see the impacts of humans and human behavior on the planet in far greater detail than before.

The COVID-19 pandemic allowed researchers to examine the effect of humans on wildlife at a larger scale and simultaneously in more habitats and on more species and trophic levels than any previous studies (Rutz et al. 2020, Tucker et al. 2023). During lockdowns there were many expected changes that were beneficial for wildlife including the following: New species appeared or increased activity in areas that were no longer disturbed by humans, there was less roadkill of smaller animals due to lower traffic, and there was less trash and pollution in many habitats (Bates et al. 2021, Manenti et al. 2020, Schrimpf et al. 2021, Tucker et al. 2023). However, there were also changes during lockdowns that were detrimental to ecosystems, including increased activity of invasive species and reduced conservation activity for threatened species (Bates et al. 2021, Manenti et al. 2020). There were also some surprising outcomes. Birds altered their songs to take advantage of lower traffic noise and sing higher performance songs (Derryberry et al. 2020). Vehicle–wildlife collisions increased during the pandemic, likely due to increased activity of larger animals that outweighed reduced traffic (Abraham & Mumma 2021). In addition, birds became less afraid of humans when they were wearing masks (Jiang et al. 2020).

Reduced movement and economic activity, especially early in the pandemic, also altered global biogeochemical cycles. This included an 8.5% reduction in global CO_2 emissions in the first half of 2020 compared to 2019, primarily from reduced ground transportation and power generation (Liu et al. 2020). However, CO_2 emissions from most countries returned to normal within 6 months. There was also a 30% reduction in NO_x and a ∼20% reduction in SO_2 emissions; these two gases have balancing effects on global temperatures (Forster et al. 2020). Overall, even with an overall reduction in CO_2 emissions of 5.5% for 2020 compared to 2019, the increase of CO_2 in the atmosphere was within the normal range of variability, indicating that the temporary and limited reduction in emissions did little to slow increasing CO_2 and global temperatures (Laughner et al. 2021, Liu et al. 2020).

One beneficial outcome of reduced contact rates among people during the first 2 years of the pandemic was an almost complete cessation of transmission of other respiratory pathogens. Specifically, during the winter of 2020–2021, restrictions to reduce the huge surge caused by the Alpha variant (**Figures 1** and **3**) had the additional secondary benefit of nearly eliminating most other respiratory illnesses, including influenza, RSV, and viruses causing the common cold. In the US, of the 1.5M clinical tests for influenza in the 2019–20 winter, before the COVID-19 pandemic, 16.8% or 250,396 were positive, whereas in the winter of 2020–21, only 2,265 or 0.8% of 1.5M tests were positive, a 95% reduction (CDC 2022a). Even in 2021–22, when restrictions in the US were substantially lower, there were fewer influenza deaths less than in any of the 10 years pre-COVID-19 in the US (CDC 2022a). In addition, over these 2 years a lineage of influenza (B/Yamagata) may have gone extinct (Koutsakos et al. 2021). Similar decreases in transmission occurred for RSV. The cumulative number of RSV hospitalizations per 100,000 people from October 1, 2019, up until April 2, 2020, was 30.3 (in the year before the COVID-19 pandemic) but only 0.2 in 2020–21, a 99% reduction!

Although there was reduced transmission of some pathogens during the pandemic, effects were not lasting, and in some cases, lower immunity due to lower transmission may have led to larger subsequent epidemics. The lack of transmission of RSV in 2020 and 2021 may have contributed to the higher than average RSV epidemic in 2022–23 which reached 45.8 hospitalizations/100,000 by the week of January 23; the 2 years pre-COVID-19 were below 19 hospitalizations/100,000 (CDC 2022b). In addition, the COVID-19 pandemic had detrimental effects on public health by limiting health care access for most populations. Cancer, tuberculosis, and HIV testing, as well as childhood vaccinations were all negatively impacted (Arsenault et al. 2022). The full impacts of the health care disruptions caused by the COVID-19 pandemic are not yet known.

CONCLUSIONS

The COVID-19 pandemic had devastating effects on multiple aspects of most human societies. However, the resources mobilized to understand and control this disease led to the creation of unparalleled data sets; new analysis tools; partnerships among scientists, government, and public health agencies; and data sharing. This deepened our understanding of the ecology and evolution of infectious diseases, especially in humans. The insights developed during the COVID-19 pandemic could provide a much stronger scientific basis for preventing, mitigating, and controlling future pandemics. Unfortunately, as during the COVID-19 pandemic, political interference and boom–bust public health funding cycles threaten to make us just as vulnerable to the next pandemic (Frieden et al. 2021).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

I thank the thousands of people who worked tirelessly to test and treat patients; track cases, hospitalizations, and deaths; sequence viruses; and more. I thank the authors and originating and submitting laboratories responsible for obtaining the specimens and generating the genetic sequences and metadata of the SARS-CoV-2 sequences in GISAID's EpiCoV database. I thank Oliver Eales and Steven Riley for sharing the data underlying **Figure 5*b***; Tom Wenseleers, Josh Schwab, and Roxanne Beltran for assistance with and feedback on manuscript figures; Theo Sanderson for guidance; and Ingrid Parker, Oliver Eales, Billy Gardner, Nikka Malakooti, and Christa Seidl for feedback on the manuscript. Financial support was received from National Science Foundation grants DEB-1911853, DEB-1717498, and CDPH-20-11088.

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