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The Ecology of Viral Emergence

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on human health, economic well-being, and societal function. It is essential that we use this generational experience to better understand the processes that underpin the emergence of COVID-19 and other zoonotic diseases. Herein, I review the mechanisms that determine why and how viruses emerge in new hosts, as well as the barriers to this process. I show that traditional studies of virus emergence have an inherent anthropocentric bias, with disease in humans considered the inevitable outcome of virus emergence, when in reality viruses are integral components of a global ecosystem characterized by continual host jumping with humans also transmitting their viruses to other animals. I illustrate these points using coronaviruses, including severe acute respiratory syndrome coronavirus 2, as a case study. I also outline the potential steps that can be followed to help mitigate and prevent future pandemics, with combating climate change a central component.

INTRODUCTION

Zoonotic diseases have been part of the human experience since the origin of our species (1). Over the expanse of evolutionary time, humans have acquired viruses by two routes, both linked to animals. The first is vertical inheritance from our closest relatives (i.e., nonhuman primates), such that viruses and hosts have codiverged over millions of years (1). Alternatively, viruses can be acquired by horizontal transfer from other animals in the process of cross-species transmission that is now a familiar cause of disease emergence. Comparative studies show that only a small subset of the approximately 250 known human viruses have been inherited from our closest ancestors, with the majority acquired by more recent cross-species transmission and hence commonly regarded as zoonotic (2).

It is also the case that the pattern and frequency of cross-species transmission have changed through time in a manner associated with major social transitions over the past 200,000 years or so (3). The small group sizes of the earliest humans associated with hunter-gathering meant that the only viruses able to sustain their transmission (i.e., generating a reproductive number, R, greater than 1) in populations were those with long durations of infection such as herpesviruses or papillomaviruses (4). As human populations became larger and denser, and interacted more with animals, from the first farmers to the birth of cities, more short-duration (i.e., acute RNA) viruses could have established themselves. Ongoing societal evolution eventually resulted in the modern age of meta-cities and rampant urbanization, global connectedness, deforestation, and climate change, a confluence of factors associated with the emergence of many diseases including human immunodeficiency virus (HIV), Ebola, and of course severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

From a virological perspective, humans and other animal species should be regarded as part of a single host pool. For emerging viruses such as SARS-CoV-2, there has been considerable debate over the identity of so-called novel hosts, reservoir hosts, and intermediate hosts that link the former two (5). However, the arc of this review is that although humans are commonly placed at the end of a chain of emergence, inherent in their typical classification of novel hosts or in discussions of zoonoses, such an anthropocentric viewpoint is misleading and may detract from the realities of infectious disease emergence and evolution. The inconvenient truth is that viruses are ubiquitous components of an increasingly threatened global ecosystem that regularly move between interacting species and more often than not have no associated disease (6, 7) (**Figure 1**). Our global distribution, rapidly growing population size, and profound environmental impact make humans increasingly impactful members of this viral ecosystem, both receiving and giving viruses to other species. SARS-CoV-2 provides a perfect example of why a new approach—considering viruses as moving parts within a global ecosystem rather than the focal points of emergence—provides a more powerful framework to view disease emergence (**Figure 1**). Herein, I address some of the traditional questions in the evolution of virus emergence before proposing a refocus centered around viewing viruses within ecosystems and using coronaviruses as a case study.

THE EVOLUTION OF VIRUS HOST RANGE

One of the long-standing questions in disease emergence is whether it is possible to identify those viruses, at least to the level of virus family or genus, that are most likely to emerge in humans. This information, it is argued, will be central to pandemic planning, perhaps facilitating the design of therapeutic interventions for a manageable range of potential pathogens prior to any future emergence event.

Much of the information now used to address this question has been derived from metagenomic (particularly total RNA) sequencing (8–10). In recent years, there has also been a move away from

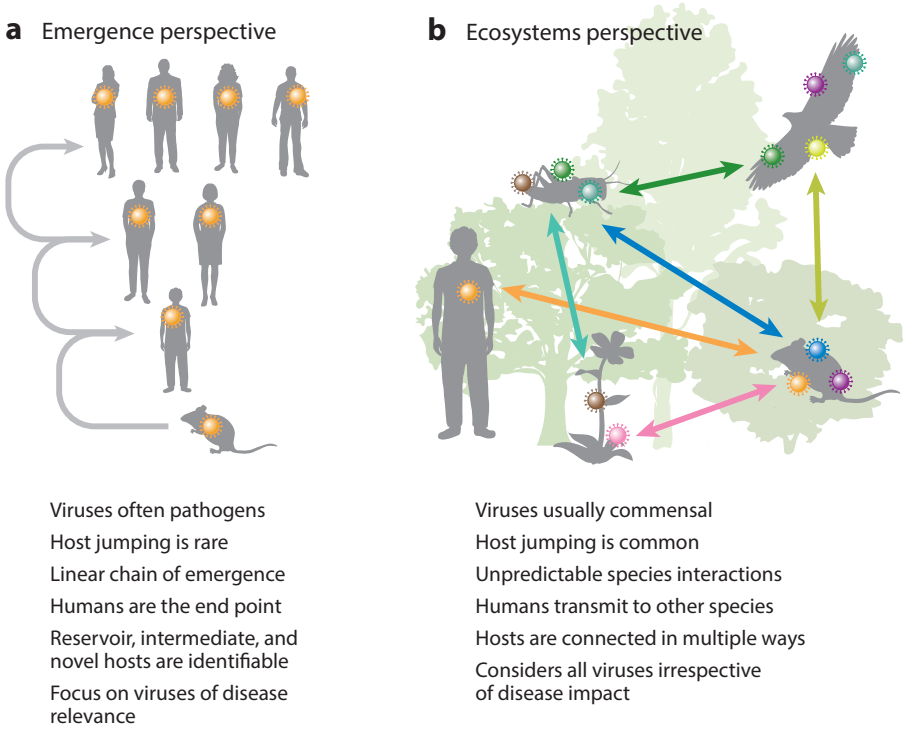


Figure 1

Characteristics of the contrasting emergence (*a*) and ecosystems (*b*) perspectives on viral emergence and zoonotic disease. Figure adapted with permission from Reference 6.

the study of diseased organisms of direct agricultural and domestic importance to humans, to more unbiased studies of seemingly healthy wildlife (8, 11). This is providing more accurate information on the true host range of viruses, and hence the determinants of virus emergence. Arguably the most striking result from these studies is that the vast majority of the animal viruses in nature remain undocumented and include an unknown number that, in the right circumstances, have the potential to emerge in human populations (12). Yet despite the magnitude of this virosphere, the greatest pandemic risk is likely posed by respiratory viruses. Their fluid mode of transmission, perhaps involving asymptomatic carriers, makes their spread efficient and control challenging. Of all the viruses described to date, three families of RNA viruses that are commonly associated with respiratory infection and that seem to regularly jump species boundaries best fit this risk profile: influenza viruses, paramyxoviruses, and coronaviruses.

Although impossible to accurately diagnose from historical records, influenza is likely an archaic infection of humans. Emergence events in humans are commonly associated with cross-species transmission from domestic poultry and/or pigs, with a wide diversity of influenza virus subtypes present in wild water birds (13, 14). Fortunately, birds and humans are sufficiently different in most virus–cell receptor specificities that avian influenza (and other avian) viruses are usually unable to successfully transmit among humans (15). Of greater concern, however, is that the documented host range of influenza viruses is increasing—or at least is better documented—including reports of the cross-species transmission of avian H9N2 influenza virus to novel hosts including Asian badgers from an artificial breeding group used to supply live animal markets in

China (16; see the section titled Preventing Future Pandemics). This again demonstrates the profound impact humans can have on disease distributions.

A paramyxovirus—measles virus—is probably one of the longest established respiratory infections of humans (17). Although the emergence of measles virus in humans may date as far back as the sixth century BCE (18), it is possible that more transmissible and/or virulent animal paramyxoviruses exist that could ultimately emerge in humans, with Hendra and Nipah viruses (genus *Henipavirus*) acting as exemplars, although to date neither have resulted in large-scale outbreaks (19, 20).

The antiquity of coronaviruses in humans is unknown. However, coronaviruses are commonly found in mammalian groups that can exist at very high population densities, including bats and rodents, or those that have strong connections with humans, such as pigs and dogs (21). They may also be spilling over in human populations at an increasing frequency (22, 23). Although the sampling of coronaviruses in nature is not extensive, even this limited sampling has shown that they can have expansive host ranges (21). This is especially true of SARS-CoV-2, with humans acting as vectors for the transmission of the virus to other animal species (24–28). At the time of writing, human-derived SARS-CoV-2 has been reported in such animals as cats, dogs, lions, tigers, puma, mink (with transmission back to humans), and particularly white-tailed deer in the United States where the virus has jumped multiple times from humans and reached level prevalence (29, 30) (**Figure 2**).

Coronaviruses, influenza virus, and paramyxoviruses are not unique in their propensity to move between hosts. Broad-scale phylogenetic analyses have shown that viruses frequently jump species boundaries on evolutionary timescales likely spanning millions of years, with cross-species transmission apparent in every virus family described to date (31) (**Figure 3**). Despite these seemingly fluid host ranges, there are a variety of genetic, immunological, and epidemiological barriers to successful virus emergence, and rates of cross-species transmission may be relatively low on the timescale of actionable public health or pandemic planning (i.e., years or decades) (32).

The initial, and most obvious, barrier to successful cross-species transmission is the encounter between humans and infected animals (including by arthropod vectors), particularly wildlife (or farmed wildlife). Modern human lifestyles, including such factors as the rise of live animal markets, are making exposure events increasingly commonplace. Following initial exposure, a virus must establish a productive infection and transmit onward in the human population. It is clear that many burgeoning outbreaks are extinguished at this point. For example, although people working in animal markets in southern China are exposed to animal coronaviruses, as is perhaps true across parts of Asia as a whole, major outbreaks are rare (33). At the level of individual hosts, the intimate relationship between virus and host cell receptor acts as a major obstacle (15), and the genetic divergence of cellular receptors along with their hosts establishes a broad phylogenetic rule in which successful host jumping is more likely among closely related hosts (1). Finally, there are an array of epidemiological constraints to productive disease emergence. For instance, if a virus emerges in a small human population, characteristic of many rural communities, then a high rate of stochastic die-out will reduce the likelihood that a virus will establish a productive transmission cycle, even for a well-adapted respiratory virus (34, 35).

MEASURING ZOONOTIC RISK

There has also been considerable interest, including detailed quantitative analyses (36–41), in determining whether some animal groups are more common sources of zoonotic viruses than others and therefore pose a greater zoonotic and pandemic risk. It has long been known that most viral infections in humans have their ancestry in mammals (42), again largely a reflection of virus–cell receptor interactions. Within the mammals, a variety of groups have served as key hosts for

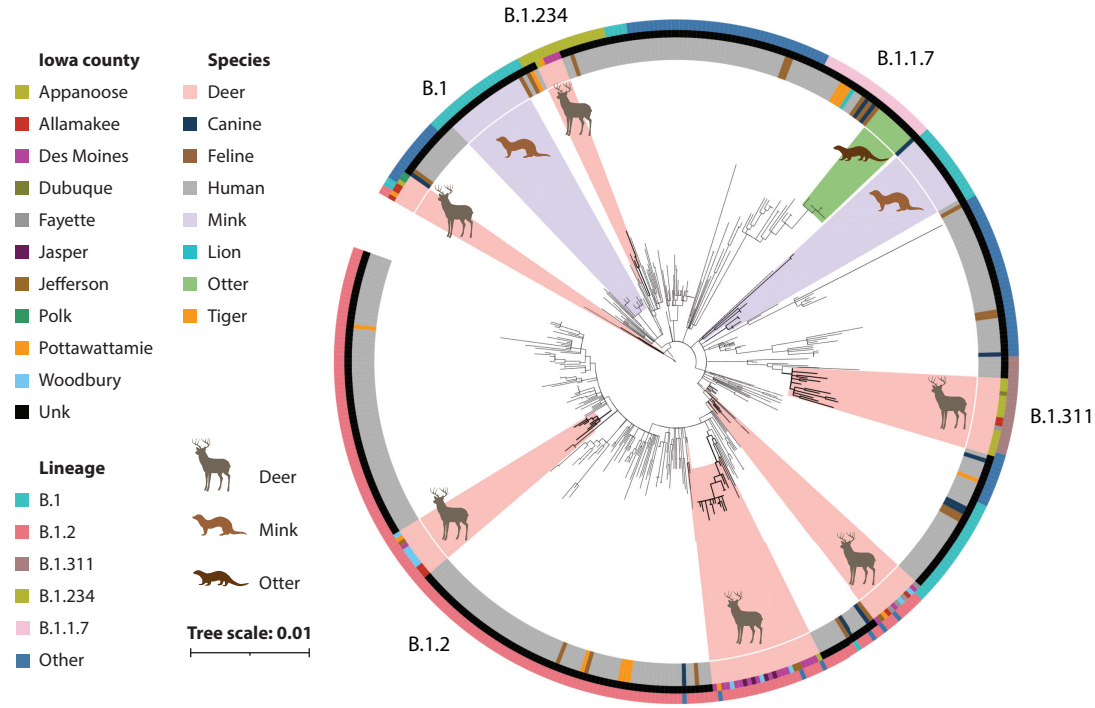


Figure 2

Multiple cross-species transmission events of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from humans to white-tailed deer in Iowa, USA. The phylogenetic tree was estimated using 94 SARS-CoV-2 genomes from white-tailed deer, 92 genomes of animal origin, and 312 human SARS-CoV-2 genome sequences from Iowa (see the color-coded legend that denotes county in Iowa, animal host, and SARS-CoV-2 lineage). Notably, the SARS-CoV-2 sequences from the white-tailed deer were closely related to those sampled from humans in Iowa but distinct from those seen in other animals such as mink. Figure adapted with permission from Reference 30 (CC BY 4.0).

zoonotic viruses, especially those with which humans share close proximity, for example, because they live near human settlements, act as food sources, or are so closely related to humans that viruses face little challenge in host adaptation.

Of most note, since the emergence of severe acute respiratory syndrome (SARS) in late 2002, there has been intense interest in bats as zoonotic hosts, and a growing number of studies have documented a wide diversity of bat viruses (43–56). For example, 30%, 24%, and 10% of the bat viruses available in the National Center for Biotechnology Information (NCBI)/GenBank database are from the *Coronaviridae*, *Rhabdoviridae*, and *Paramyxoviridae* families of RNA viruses, respectively (57) (**Figure 4**). However, an important caveat is that rather than infecting bats themselves, many of the viruses detected in bats may instead be associated with aspects of their diet or microbiome, such that host range can be hard to determine from genomic data alone (57). Initial investigations during the SARS epidemic of 2002–2003 showed that captive masked palm civets (*Paguma larvata*) were the probable source of the virus, with disease emergence associated with their presence in live animal markets in southern China (58, 59). SARS-like coronaviruses were later identified in bats of the genus *Rhinolophus* (i.e., horseshoe bats) in various Chinese provinces, with onward transmission to civets (and perhaps raccoon dogs), which then seeded human infection (60–63). Bats similarly played a key role in the ecology of Middle East respiratory syndrome coronavirus (MERS-CoV), first described in Saudi Arabia in 2012 (64). Although multiple

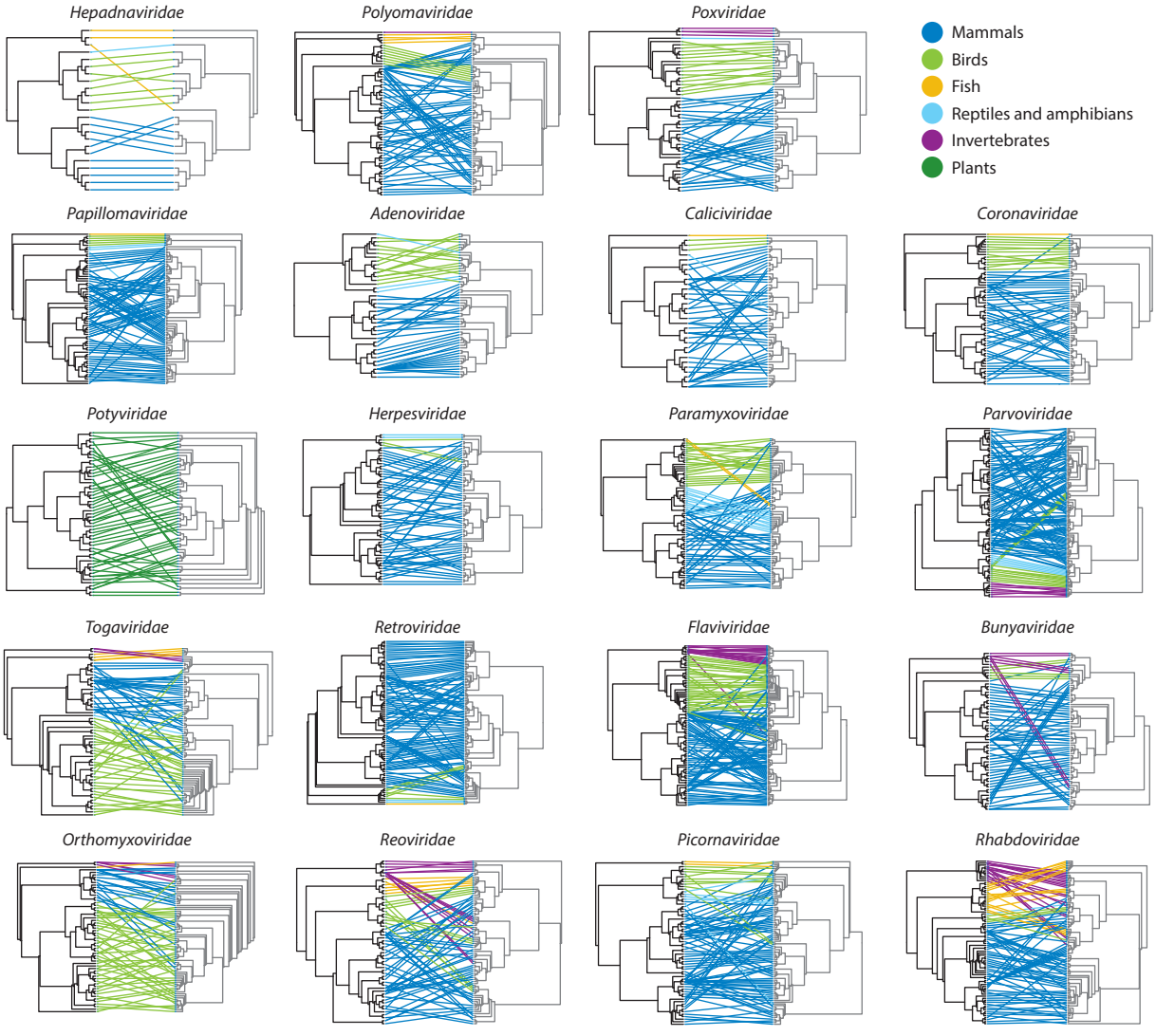
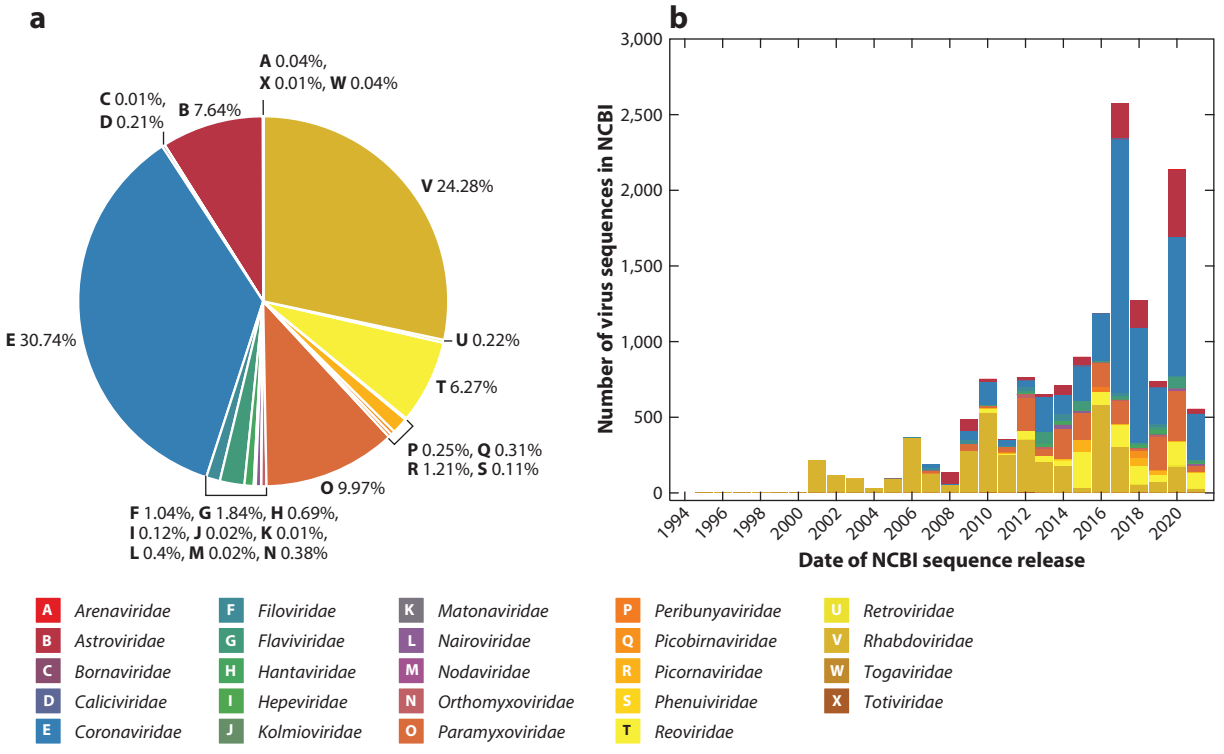


Figure 3

Frequent virus cross-species transmission among hosts on evolutionary timescales. The figure shows tanglegrams of phylogenetic trees of 19 families of DNA and RNA viruses. Lines connecting the host (*left*) with its virus (*right*) are colored according to the host type (*dark blue*: mammals; *light green*: birds; *light blue*: reptiles and amphibians; *gold*: fish; *purple*: invertebrates; *dark green*: plants). Crossed lines between trees are indicative of host jumping. On this sample of viruses the lowest frequency of cross-species transmission is found in the *Hepadnaviridae*, while the highest frequency is found in the *Rhabdoviridae*. Note that cross-species transmission in the *Coronaviridae* is commonplace with each vertebrate class (especially the mammals) but rare between classes. Figure adapted with permission from Reference 31 (CC BY 4.0).

MERS-CoV-like lineages reflecting several decades of circulation were identified in dromedary camels, with transmission events to humans (65), MERS-like coronaviruses were later identified in multiple bat species, although with different cell receptor usage (66–69).

Bats are clearly hosts for a large and diverse array of viruses from multiple families, some of which have jumped species boundaries to emerge in new hosts and very occasionally cause disease



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

The diversity of viruses found in bats (mammalian order *Chiroptera*). The figure utilizes the sequences of bat viruses publicly available in the National Center for Biotechnology Information (NCBI)/GenBank database. (*a*) The percentage of bat virus sequences from families of RNA viruses. (*b*) RNA virus sequences by year of NCBI release. (*c*) The percentage of bat virus sequences that belong to families of DNA viruses. (*d*) DNA virus sequences by year of NCBI release. Figure adapted with permission from Reference 57 (CC BY-NC-ND 4.0).

outbreaks. Although there have been a variety of proposals, the biological reasons that underpin the diverse and abundant bat virome are not yet fully understood (48, 70, 71). A popular theory is that the distinctive immunological traits of bats, such as differences in the number and expression patterns of interferon genes, may in large part explain why bats are often asymptomatic carriers for myriad viruses (52, 72, 73). The social structure of bat populations, sometimes (depending on the species) involving very large roosting numbers and species cohabitation, similarly provides the perfect setting for viral transmission, and large and dense populations are expected to carry more viruses including those of elevated virulence because susceptible hosts are more abundant (74). In addition, the capacity of bats to travel large distances, even on a nightly basis, provides a mechanism for viruses to become established in naïve bat populations.

Despite this, the increasing frequency with which bat viruses are described is undoubtedly impacted by major ascertainment and confirmation biases (75, 76). Some studies suggest that bats carry no more viruses than expected given their species richness (39). Such biases will have a major impact on the accuracy of zoonotic risk assessment, perhaps making it naïve to focus on bats to the exclusion of other mammalian taxa. More importantly, bat viruses rarely establish successful human infection, and most bat viruses are not transmitted to humans (57). Rather, bat-to-human transmission routinely involves other animal hosts (such as civets), again highlighting the importance of considering viral ecosystems in their entirety. Similarly, the zoonotic risk posed by bat viruses should be qualified by the observation that some virus families have likely been associated with bats for many thousands or millions of years (77). However, it is possible that the rate of human spillover has increased with greater human encroachment into bat habitats. In short, while bats are undoubtedly important players in disease emergence, they are only one component of the far more complex global viral ecosystem.

RECOMBINATION AND VIRAL EMERGENCE

All virus families—both RNA and DNA—are marked by frequent cross-species transmission on evolutionary timescales (31) (**Figure 3**). Despite this, it has been suggested that because recombination creates new genomic configurations, those viruses that recombine at the highest frequencies are better able to jump species boundaries (1). For example, viruses on the evolutionary lineage containing SARS-CoV-2—members of the subgenus *Sarbecovirus*—have a complex history of recombination, particularly involving multiple bat coronaviruses (78); the complexity of these events makes it challenging to even determine the exact parental viral lineages (79). Coronaviruses as a group are characterized by relatively high rates of recombination for RNA viruses, likely because subgenomic negative-sense RNAs are generated through copy choice template switching of the RNA-dependent RNA polymerase as a means of controlling gene expression (80).

While it is obvious that recombination generates genetic diversity, it is also the case that most recombinants, like most point mutations, will be deleterious and hence reduce fitness. Indeed, most animal viruses contain mutations that render them incapable of human infection. Similarly, recombination among animal viruses will rarely increase likelihood of emergence. It may also be that the rate of (point) mutation is so high in most RNA viruses—approximating one mutation per round of genome replication, with many replication cycles during an individual infection and very

high levels of viral progeny (81)—that recombination adds little adaptive value. For this reason, it has been argued that recombination in RNA viruses did not evolve to generate genetic diversity but rather is a mechanistic by-product of particular forms of genome organization (82).

More importantly, there is no overall association between the ability to recombine and the ability of zoonotic viruses to emerge in humans. Coronaviruses do not have especially high rates of cross-species transmission in comparison to other RNA viruses (**Figure 3**), and have seemingly lower rates than those seen in families such as the *Rhabdoviridae*, *Flaviviridae*, and *Paramyxoviridae*, which are characterized by very low rates of recombination. Hence, on evolutionary timescales, there is no association between the frequency of recombination and the ability of any individual family to jump species boundaries (83). Rather, the true risk posed by coronaviruses and influenza is because they are often associated with respiratory infection and hence are easily transmitted.

ZOONOSIS AND VIRULENCE

Another of the most challenging questions in disease emergence is how the virulence of the virus will evolve following its emergence in the new host. Once again, this is an issue that has come into play with SARS-CoV-2 (84). Although it is often proposed that viruses inevitably evolve to lower virulence, as host death is thought to be detrimental to virus fitness, the true picture is far more complex. Indeed, predicting the long-term evolution of virulence is a perilous task that requires a nuanced understanding of virus biology at both the intra- and interhost levels that is rarely achieved (85, 86).

It is usually thought that natural selection favors the level of virulence that maximizes transmission, as transmission is a surrogate of reproductive number. However, the exact relationship between transmission and virulence can be difficult to determine and does not necessarily take the form of an evolutionary trade-off (in which one parameter increases as the other decreases) as is often proposed (86). Depending on the precise relationship between virulence and transmissibility, it is possible that virulence will increase, decrease, or stay the same through time. An example of such inherent complexity is provided by two of the viruses released as biological controls to eliminate invasive European rabbits in Australia. The first strains of myxoma virus (MYXV; a large double-stranded DNA virus) released in 1950 killed a remarkable ~99.8% of rabbits (87). Yet within a few years the virus had evolved to lower levels of virulence, with a mean mortality rate of ~50%, although with considerable variation (and evolved host resistance). Both highly virulent and attenuated strains are sampled in nature today (87). The biological explanation for this virulence decline is that MYXV is primarily transmitted by mosquitoes and fleas that bite skin lesions on live rabbits so that high mortality reduces transmission rates and hence fitness. In contrast, rabbit hemorrhagic disease virus (RHDV; a positive-sense RNA virus) released into the rabbit population in the mid-1990s appears to have experienced an increase in virulence, presumably because in Australia the virus is commonly transmitted by blow flies that feed on rabbit carcasses, in which case high levels of mortality bolster transmission rates (88).

Most highly transmissible respiratory viruses in humans tend to have relatively low levels of virulence, at least in comparison to pathogens such as MYXV and HIV, presumably because fitness is enhanced by having hosts that are mobile and so are able to continue transmission. The evolution of virulence in respiratory viruses might also be impacted by the physical location of the cell types infected (84). A simple division can be made between viruses that infect cells of the upper respiratory tract that impact transmission most directly—because the viruses from these cells are shed more frequently—and those that infect cells of the lower respiratory tract (including the lungs) that will result in the most severe disease. A virus able to infect both cell types, which may differ in the nuances of receptor binding, will likely simultaneously increase both transmissibility

and virulence, arguably as seen with both the Alpha and Delta SARS-CoV-2 variants of concern (84). In contrast, a virus that preferentially infects the upper over the lower respiratory tract to enhance transmission would also lower virulence. This appears to be true of the Omicron variant of concern (89–91), while the highly pathogenic subtypes (particularly H5 and H7) of avian influenza virus that preferentially replicate in cells of the human lower respiratory track demonstrate the opposite scenario and likely explain their lack of sustained human-to-human transmission (15, 92).

AN ECOSYSTEMS PERSPECTIVE ON DISEASE EMERGENCE

The COVID-19 pandemic has brought an understandable focus on the emergence of zoonotic diseases. There is, however, a danger that it may also paint a false picture of virus evolution and ecology, particularly the timescale and the directionality of host jumping events. To fully understand the factors that cause disease emergence and prevent future zoonotic events, it is pivotal to acknowledge that viruses have been an integral component of global ecosystems well before becoming clinically and agriculturally relevant, and that disease emergence is strongly associated with ecological disturbance (**Figure 1**). Given that humans are an increasingly important part of the global ecosystem that encompasses viruses, the central issue is not that zoonotic viruses appear in humans, but rather the seemingly increasing frequency of this process and how it is impacted by human society today.

The transition to thinking about viruses from the perspective of ecosystems extends the popular One Health concept (93). While One Health largely focuses on viruses as agents of disease, particularly linking those diseases in humans and animals, the ecosystems perspective is broader. It considers the totality of viruses, including those that have established commensal relationships with their hosts, as well as the factors that perturb ecosystems and hence impact the risk of disease emergence, as well as the intertwined consequences that follow ecological disturbance (6).

A core concept of the ecosystems approach is that the zoonotic transmission of viruses to humans is a common and expected occurrence, but only in rare cases does this lead to disease outbreaks. Indeed, metagenomic studies consistently show that healthy animal species can carry a multitude of viruses with no apparent disease consequences (32), although the underlying reasons are not clear. The viruses of most research interest to virologists were traditionally those that infect either humans or domesticated animals and plants that are of most importance to human society. While this anthropocentric bias is understandable, it has perhaps led to a lack of appreciation of the magnitude and connectedness of the global virosphere. The natural tendency is to consider humans as the end point of an evolutionary process, and the term zoonosis itself has an inherent directionality: Viruses have animal reservoirs, which represent the source population, and then jump to humans as novel hosts. However, although all human viruses have their ultimate ancestry in those found in other animals, humans are not exclusively recipient hosts (**Figure 1**). An illustrative case in point is provided by influenza virus. It is textbook knowledge that pigs commonly carry (swine) influenza viruses, some of which have the ability to emerge in humans (92). Indeed, pigs have been implicated in many influenza pandemics, including the H1N1 pandemic of 2009 (94). Interestingly, in the years immediately preceding the emergence of H1N1 in humans, closely related H1N1 viruses with similar triple reassortant genomic configurations occasionally spilled over from pigs to humans in the United States (95). Although this fits the narrative that humans are at the end of the emergence pathway, large-scale phylogenetic studies reveal that influenza viruses more commonly jump from humans to pigs than from pigs to humans (96), confusing our notion of reservoir and novel hosts. The virus ecosystem is expansive and complex, with myriad connections between hosts, of which humans are but a small but highly impactful component.

Placing disease emergence within an ecological context will also lead to a new appreciation of the complexity and unpredictability of events that take place following ecosystem disturbance,

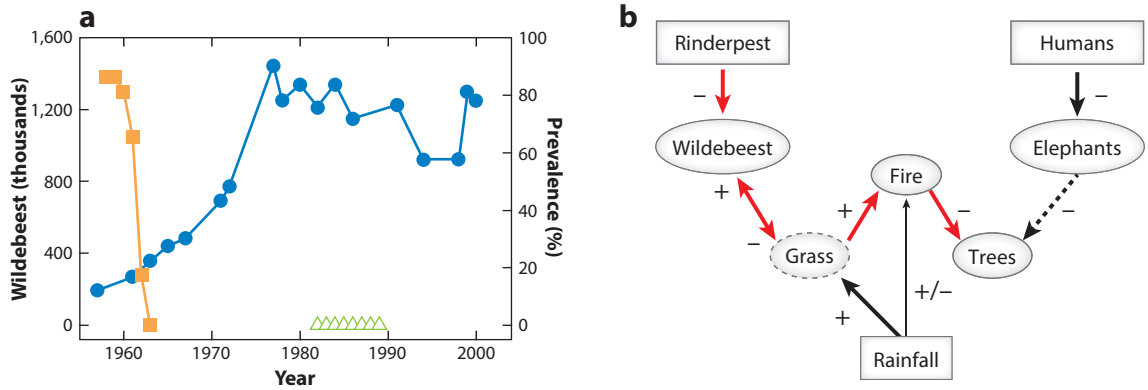


Figure 5

How viral diseases impact ecosystems—the case of rinderpest in the Serengeti. (*a*) The population size of wildebeest in the Serengeti (*blue circles*) from 1958 to 2000 as well as the seroprevalence of rinderpest (caused by a paramyxovirus; *orange squares*) during 1958–1963. Note that the rise of wildebeest numbers is associated with the earlier decline of rinderpest. (*b*) The relationships between key ecosystem components, and particularly how they impact tree population dynamics, a major carbon sink. Thick arrows denote the dominant effects. A causal pathway linking rinderpest with tree population numbers is shown in red. The dotted outline denotes the grass compartment. Figure adapted with permission from Reference 98 (CC BY 4.0).

rather than the linear sequence of events implicit in emergence narratives (97). The paramyxovirus rinderpest virus caused a disease epidemic in East Africa (including the Serengeti) in the 1890s, leading to a reduction in the size of wildebeest and buffalo populations (6). This lowered grazing pressure, leading to more fires that suppressed the establishment of trees, in turn reducing a major carbon sink, and changing the ecosystem from woodland to grassland (**Figure 5**). Remarkably, the reduction in grazing mammals also led to tsetse flies (*Glossina* spp.) switching their prey to humans, resulting in an epidemic of the parasitic disease African trypanosomiasis (97). However, the ecosystem reverted to a woodland state when rinderpest was eradicated through vaccination and the number of fires was reduced (98). Similarly, the hunting (or not) of puma in North America has been proposed to impact the transmission of and selection pressures acting on feline immunodeficiency virus (99).

The adoption of an ecological perspective will help us better understand how climate change will impact disease emergence (100) (**Figure 1**). Warming global temperatures will inevitably result in changing geographic distributions of animal populations as appropriate habitats shrink. This may lead to greater interspecies contact, fueling cross-species virus transmission. Those human populations that rely most intimately on the animal world will also find their livelihoods compromised, and so they may change farming practices or exploit novel or more ecosystem resources, again elevating the risk of exposure to animals and their pathogens, driving disease emergence (101, 102). One group of viruses for which climate change is of obvious importance are those transmitted by arthropod vectors (i.e., arboviruses). A warming climate is strongly associated with an expanding home range for mosquitoes, enabling their spread to currently more temperate regions of the planet (103–105). We should therefore expect diseases such as dengue and Zika to make more regular appearances at more temperature latitudes.

A reduction in biodiversity through climate change may also increase the rate by which vector-borne diseases emerge by limiting the dilution effect (106–108). Under this theory, increasing species richness reduces disease risk, particularly when the most competent hosts for a particular

vector dominate the ecosystem and hence draw (dilute) more pathogen transmission than less competent hosts (108). Habitat destruction and ecosystem disturbance due to changes in land use inevitably contribute to the loss of biodiversity, and it is possible that this will directly impact disease emergence. Conversely, pandemics also have a major environmental impact, with, for example, the COVID-19 pandemic generating an enormous amount of plastic waste (109, 110).

THE EMERGENCE OF SARS-CoV-2

The betacoronavirus SARS-CoV-2 was first reported in association with severe pneumonia in the Chinese city of Wuhan in December 2019 (111–113). Although some undetected transmission is inevitable, there is no convincing evidence for its presence prior to this date, and time estimates from molecular clock dating suggest that the known diversity of SARS-CoV-2 likely has a common ancestor no earlier than November 2019 (114). Although there have been suggestions that SARS-CoV-2 was in some European countries, particularly Italy, earlier in 2019, these remain unconvincing, especially as they would have been expected to seed larger European outbreaks (115). Retrospective studies of influenza-like illnesses in Wuhan have failed to detect SARS-CoV-2 before late 2019 (116), while a metagenomic analysis of patients presenting with respiratory disease at Wuhan Central Hospital during 2016 and 2017 similarly did not detect the virus (117).

Like SARS-CoV in southern China before it, the emergence of SARS-CoV-2 was strongly linked to a market selling live animals (118). Indeed, there is mounting evidence that the Huanan Seafood Wholesale Market in Wuhan played a key role in the emergence of SARS-CoV-2 (119). Many, although not all, of the earliest cases of COVID-19 were associated with this market (118). Of equal importance, some of the key wildlife species previously involved in the emergence of SARS-CoV were sold in the Huanan market and other markets in Wuhan at the time SARS-CoV-2 was first described, including raccoon dogs (*Nyctereutes procyonoides*) (120). These carnivores, both captured from the wild and farmed, are known to be susceptible to infection with SARS-CoV-2 (121, 122). Thus, that the emergence of SARS-CoV-2 might be associated with a live animal market should come as no surprise from an ecological perspective. There is now ample evidence that the game animals sold at markets in China, including raccoon dogs, very commonly carry viruses, and that some have likely jumped hosts in the recent past (16). It is therefore clear that live animal markets, like the Huanan market, act as ecological mixing zones with the potential to fuel future pandemics.

As soon as the first genome sequence of SARS-CoV-2 was made available, it was obvious that the virus was closely related to both SARS-CoV and a number of sarbecoviruses found in bats (110). Subsequent metagenomic surveys identified viruses closely related to SARS-CoV-2 in *Rhinolophus* bat species from several Asian countries (China, Cambodia, Thailand, Japan, and Laos) (123–128). Remarkably, 26 novel bat coronaviruses, including two of the closest relatives of SARS-CoV-2 (RpYN06 and RnYN02), were sampled at a 1,100-ha tropical botanic garden in Yunnan Province, China (129, 130). Given how common *Rhinolophus* bats are across parts of Asia (130), it is inevitable that more viruses closely related to SARS-CoV-2 will be identified in these animals. As a case in point, SARS-CoV-related coronaviruses were recently identified in *Rhinolophus malayanus*, *R. pusillus* and *R. marshalli* from Laos, three of which were closely related to SARS-CoV-2 and possessed a receptor binding domain (RBD) in the virus spike protein with high similarity to that of SARS-CoV-2 and the ability to bind to the human ACE2 receptor (127). Notably, one of these viruses, denoted Banal-20-52, is the closest relative of SARS-CoV-2 documented to date, exhibiting 96.8% sequence similarity (127). This provides compelling evidence that viruses with a functional core equivalent to that of SARS-CoV-2, and hence capacity to infect humans, exist in wildlife species.

Far more surprising was the detection of viruses related to SARS-CoV-2 in pangolins (131). At the time of writing, these are the only other mammalian species known to carry a close relative of SARS-CoV-2 not derived through spill-back from humans. Prior to the emergence of SARS-CoV-2, very little was known about the viruses carried by these highly trafficked and endangered animals (132). Not only was the presence of SARS-CoV-2 in pangolins unexpected, but also it was characterized by some unusual features. First, the viruses were sampled not from native Chinese pangolins but rather from diseased Malayan pangolins (*Manis javanica*) illegally smuggled into China and confiscated by provincial customs authorities (131). Hence, SARS-CoV-2-like viruses are found in mammalian species potentially associated with the wildlife trade. Second, there are two distinct, although related, lineages of pangolin SARS-CoV-2-like virus, associated with those animals confiscated in Guangdong and Guangxi Provinces, respectively (131). Of these, the Guangdong pangolin coronavirus is closer to SARS-CoV-2, particularly in the RBD (128, 131). Despite this, the role of pangolins, if any, in the genesis and emergence of SARS-CoV-2 remains uncertain. The existence of multiple virus lineages in pangolins, both closely related to SARS-CoV-2, argues for a more long-standing association. However, it is possible that they represent ecological sinks that did not transmit their viruses onto other species and perhaps were simply the victims of transient spillover infections from other hosts. Irrespective of the ultimate role of pangolins, it is highly unlikely that the host range of SARS-CoV-2-like viruses in nature simply comprises bats and pangolins.

PREVENTING FUTURE PANDEMICS

That we live in an ecosystem of interacting virus hosts with an increasingly porous animal-human interface makes future zoonotic outbreaks, epidemics, and pandemics an inevitability we must be prepared to counter (133).

It does not take profound insight to realize that more intensive and effective surveillance at the animal-human interface is the simplest, and probably most effective, way to mitigate and prevent future pandemics. Given its capacity to detect recent and past infection, such surveillance is most effectively performed using immunological tools, perhaps using approaches such as VirScan (134), adapted to recognize peptides from those groups of viruses, such as coronaviruses, influenza viruses, and paramyxoviruses, that arguably have the greatest pandemic potential. This could be combined with ongoing metagenomic surveillance to detect active infections, although this technology is more costly, especially for low-income countries, and similarly more computationally intensive.

Once appropriate tools are available, surveillance should be performed in a variety of groups that most directly represent the human-animal interface (76, 135). Of special importance is the wildlife trade and its downstream end point—live animal markets such as the Huanan market in Wuhan. As noted above, recent metagenomic surveillance of the animal breeding facilities that supply these markets in China has identified a huge diversity of viruses, including novel coronaviruses and influenza viruses, as well as those that have recently jumped species barriers (16). There also remains a flourishing national and international trade in bushmeat despite its role in the emergence of viruses such as HIV (136, 137). Hence, surveillance of those (humans and animals) involved in the wildlife trade and its farming, as well as those who work at live animal markets or are involved in animal hunting and the bushmeat trade, should be a priority. Any such surveillance system could be placed within a pandemic radar, in which information on sporadic zoonotic events to full-blown disease outbreaks is shared more rapidly and more freely than is done today (138). This should involve not only the immunological and genomic surveillance described above but also a new infrastructure to enable rapid genome sequencing of any rapidly spreading pathogen.

In contrast, the large-scale sampling and genomic surveillance of healthy wildlife species in nature are unlikely to be practical (135). As already noted, wildlife species harbor a vast and continually evolving pool of viruses that will differ by tissue type and time of sampling, and across the home range of any particular species, such that a full inventory of viruses from supposed risk species is unattainable. Similarly, determining whether any of this vast animal virosphere can infect human cells requires very time-consuming and costly laboratory work (32). Given the rapidity of virus evolution in nature, it would also be the case that any such wildlife surveillance would need to be repeated on a continuing basis.

As well as surveillance, a variety of other measures can be adopted to limit the risk of future zoonotic events. First and foremost, we need to better separate ourselves from wildlife, reducing the species overlap that shapes viral ecology and that is the key interface for emerging infectious disease. In particular, the wildlife trade and the live animal markets it supplies must be strongly regulated and monitored. More broadly, authorities should be discouraged from approving building in green areas commonly used by wildlife species of bats, and effort should be devoted to establishing and maintaining suitable and sustainable environments for wildlife, including bats, located away from population centers (139). Establishing a better ecology for animals and enhancing ecosystem biodiversity will do much to reduce the risk of human infection.

CONCLUDING REMARKS

It has been almost 40 years since the first description of HIV-1 as the cause of acquired immunodeficiency syndrome (AIDS) (140). In the decade following it became clear that HIV/AIDS was itself a zoonotic disease that had jumped to humans from an animal reservoir (i.e., chimpanzees), with a cause based on ecosystem disturbance—logging at the start of the twentieth century and the rise of bushmeat consumption (141, 142). The discovery of HIV also heralded a new interest in studies of disease emergence. Despite the huge amount of data generated, it is now time to move away from thinking of disease emergence as solely an evolutionary process to thinking of it as an ecological one, without a clear directionality and in which humans play an increasingly important part. Only through the lens of ecology will we be able to reveal the true frequency with which viruses jump species boundaries, the determinants of this process, the role played by humans, and the pandemic risks of the future—and how these might be mitigated. Most of all, we should acknowledge that pandemics and climate change are partners in crime. Unless we act now to counter global climate change and its profound ecological consequences, COVID-19 will be only a forewarning of what is to come.

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LITERATURE CITED

1. Holmes EC. 2009. *The Evolution and Emergence of RNA Viruses*. Oxford, UK: Oxford Univ. Press
2. Woolhouse ME, Haydon DT, Antia R. 2005. Emerging pathogens: the epidemiology and evolution of species jumps. *Trends Ecol. Evol.* 20:238–44

3. Cleaveland S, Haydon DT, Taylor L. 2007. Overviews of pathogen emergence: Which pathogens emerge, when and why? *Curr. Top. Microbiol. Immunol.* 315:85–111
4. Black FL. 1975. Infectious diseases in primitive societies. *Science* 187:515–18
5. Hu B, Guo H, Zhou P, Shi ZL. 2021. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* 19:141–54
6. French RK, Holmes EC. 2020. An ecosystems perspective on virus evolution and emergence. *Trends Microbiol.* 28:165–75
7. Roossinck MJ. 2015. Plants, viruses and the environment: ecology and mutualism. *Virology* 479:271–77
8. Delwart E. 2012. Animal virus discovery: improving animal health, understanding zoonoses, and opportunities for vaccine development. *Curr. Opin. Virol.* 2:344–52
9. Zhang Y-Z, Chen Y-M, Wang W, Qin X-C, Holmes EC. 2019. Expanding the RNA virosphere by unbiased metagenomics. *Annu. Rev. Virol.* 6:119–39
10. Zhang YZ, Shi M, Holmes EC. 2018. Using metagenomics to characterize an expanding virosphere. *Cell* 172:1168–72
11. Shi M, Lin X-D, Chen X, Tian J-H, Chen L-J, et al. 2018. The evolutionary history of vertebrate RNA viruses. *Nature* 556:197–202
12. Carlson CJ, Zipfel CM, Garnier R, Bansal S. 2019. Global estimates of mammalian viral diversity accounting for host sharing. *Nat. Ecol. Evol.* 3:1070–75
13. Peiris JS, de Jong MD, Guan Y. 2007. Avian influenza virus (H5N1): a threat to human health. *Clin. Microbiol. Rev.* 20:243–67
14. Taubenberger JK, Kash JC. 2010. Influenza virus evolution, host adaptation and pandemic formation. *Cell Host Microbe* 7:440–51
15. Baigent SJ, McCauley JW. 2003. Influenza type A in humans, mammals and birds: determinants of virus virulence, host-range and interspecies transmission. *Bioessays* 25:657–71
16. He W-T, Hou X, Zhao J, Sun J, He H, et al. 2022. Virome characterization of game animals in China reveals a spectrum of emerging viral pathogens. *Cell* 185:1117–29.e8
17. Dobson AP, Carper ER. 1996. Infectious diseases and human population history. *Bioscience* 46:115–26
18. Düx A, Lequime S, Patrono LV, Vrancken B, Boral S, et al. 2020. Measles virus and rinderpest virus divergence dated to the sixth century BCE. *Science* 368:1367–70
19. Field HE, Mackenzie JS, Daszak P. 2007. Henipaviruses: emerging paramyxoviruses associated with fruit bats. *Curr. Top. Microbiol. Immunol.* 315:133–59
20. Yob JM, Field H, Rashdi AM, Morrissy C, van der Heide B, et al. 2001. Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia. *Emerg. Infect. Dis.* 7:439–41
21. Corman VM, Muth D, Niemeyer D, Drosten C. 2018. Hosts and sources of endemic human coronaviruses. *Adv. Virus Res.* 100:163–88
22. Lednicky JA, Tagliamonte MS, White SK, Elbadry MA, Alam MM, et al. 2021. Independent infections of porcine deltacoronavirus among Haitian children. *Nature* 600:133–37
23. Vlasova AN, Diaz A, Damtie D, Xiu L, Toh T-H, et al. 2022. Novel canine coronavirus isolated from a hospitalized patient with pneumonia in east Malaysia. *Clin. Infect. Dis.* 74:446–54
24. Mahdy MAA, Younis W, Ewaida Z. 2020. An overview of SARS-CoV-2 and animal infection. *Front. Vet. Sci.* 7:596391
25. McAloose D, Laverack M, Wang L, Killian ML, Caserta LC, et al. 2020. From people to *Panthera*: natural SARS-CoV-2 infection in tigers and lions at the Bronx Zoo. *mBio* 11:e02220-20
26. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, et al. 2021. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. *Science* 371:172–77
27. van Aart AE, Velkers FC, Fischer EAJ, Broens EM, Egberink H, et al. 2021. SARS-CoV-2 infection in cats and dogs in infected mink farms. *Transbound. Emerg. Dis.* **https://doi.org/10.1111/tbed.14173**
28. Koeppel KN, Mendes A, Strydom A, Rotherham L, Mulumba M, Venter M. 2022. SARS-CoV-2 reverse zoonoses to pumas and lions, South Africa. *Viruses* 14:120
29. Chandler JC, Bevins SN, Ellis JW, Linder TJ, Tell RM, et al. 2021. SARS-CoV-2 exposure in wild white-tailed deer (*Odocoileus virginianus*). *PNAS* 118:e2114828118
30. Kuchipudi SV, Surendran-Nair M, Ruden RM, Yon M, Nissly RH, et al. 2022. Multiple spillovers from humans and onward transmission of SARS-CoV-2 in white-tailed deer. *PNAS* 119:e2121644119

31. Geoghegan JL, Duchêne S, Holmes EC. 2017. Comparative analysis estimates the relative frequencies of co-divergence and cross-species transmission within viral families. *PLOS Pathog*. 13:e1006215
32. Harvey E, Holmes EC. 2022. Diversity and evolution of the animal virome. *Nat. Rev. Microbiol.* 20:321–34
33. CDC (Cent. Dis. Control Prev.). 2003. Prevalence of IgG antibody to SARS-associated coronavirus in animal traders–Guangdong Province, China, 2003. *MMWR Morb. Mortal. Wkly. Rep*. 52:986–87
34. Antia R, Regoes RR, Koella JC, Bergstrom CT. 2003. The role of evolution in the emergence of infectious diseases. *Nature* 426:658–61
35. Wasik BR, de Wit E, Munster V, Lloyd-Smith JO, Martinez-Sobrido L, Parrish CR. 2019. Onward transmission of viruses: How do viruses emerge to cause epidemics after spillover? *Philos. Trans. R. Soc. B* 374:20190017
36. Albery GF, Becker DJ, Brierley L, Brook CE, Christofferson RC, et al. 2021. The science of the host-virus network. *Nat. Microbiol.* 6:1483–92
37. Becker DJ, Albery GF, Sjodin AR, Poisot T, Bergner LM, et al. 2022. Optimising predictive models to prioritise viral discovery in zoonotic reservoirs. *Lancet Microbe.* **https://doi.org/10.1016/S2666-5247(21)00245-7**
38. Carlson CJ, Farrell MJ, Grange Z, Han BA, Mollentze N, et al. 2021. The future of zoonotic risk prediction. *Philos. Trans. R. Soc. B* 376:20200358
39. Mollentze N, Streicker DG. 2020. Viral zoonotic risk is homogenous among taxonomic orders of mammalian and avian reservoir hosts. *PNAS* 117:9423–30
40. Mollentze N, Babayan SA, Streicker DG. 2021. Identifying and prioritizing potential human-infecting viruses from their genome sequences. *PLOS Biol*. 19:e3001390
41. Olival KJ, Hosseini PR, Zambrana-Torrelio C, Ross N, Bogich TL, et al. 2017. Host and viral traits predict zoonotic spillover from mammals. *Nature* 546:646–50
42. Luis AD, Hayman DT, O'Shea TJ, Cryan PM, Gilbert AT, et al. 2013. A comparison of bats and rodents as reservoirs of zoonotic viruses: Are bats special? *Proc. Biol. Sci.* 280:20122753
43. Anthony SJ, Johnson CK, Greig DJ, Kramer S, Che X, et al. 2017. Global patterns in coronavirus diversity. *Virus Evol*. 3:vex012
44. Bergner LM, Orton RJ, Broos A, Tello C, Becker DJ, et al. 2021. Diversification of mammalian deltaviruses by host shifting. *PNAS* 118:e2019907118
45. Donaldson EF, Haskew AN, Gates JE, Huynh J, Moore CJ, Frieman MB. 2010. Metagenomic analysis of the viromes of three North American bat species: viral diversity among different bat species that share a common habitat. *J. Virol.* 84:13004–18
46. Ge X, Li Y, Yang X, Zhang H, Zhou P, et al. 2012. Metagenomic analysis of viruses from bat fecal samples reveals many novel viruses in insectivorous bats in China. *J. Virol.* 86:4620–30
47. Hardmeier I, Aeberhard N, Qi W, Schoenbaechler K, Kraettli H, et al. 2021. Metagenomic analysis of fecal and tissue samples from 18 endemic bat species in Switzerland revealed a diverse virus composition including potentially zoonotic viruses. *PLOS ONE* 16:e0252534
48. Kohl C, Brinkmann A, Radonić A, Dabrowski PW, Mühldorfer K, et al. 2021. The virome of German bats: comparing virus discovery approaches. *Sci. Rep.* 11:7430
49. Letko M, Seifert SN, Olival KJ, Plowright RK, Munster VJ. 2020. Bat-borne virus diversity, spillover and emergence. *Nat. Rev. Microbiol.* 18:461–71
50. Li L, Victoria JG, Wang C, Jones M, Fellers GM, et al. 2010. Bat guano virome: predominance of dietary viruses from insects and plants plus novel mammalian viruses. *J. Virol.* 84:6955–65
51. Mendenhall IH, Wen DLH, Jayakumar J, Gunalan V, Wang L, et al. 2019. Diversity and evolution of viral pathogen community in cave nectar bats (*Eonycteris spelaea*). *Viruses* 11:250
52. Smith I, Wang LF. 2013. Bats and their virome: an important source of emerging viruses capable of infecting humans. *Curr. Opin. Virol.* 3:84–91
53. Wu Z, Yang L, Ren X, He G, Zhang J, et al. 2016. Deciphering the bat virome catalog to better understand the ecological diversity of bat viruses and the bat origin of emerging infectious diseases. *ISME J.* 10:609–20
54. Wu Z, Ren X, Yang L, Hu Y, Yang J, et al. 2012. Virome analysis for identification of novel mammalian viruses in bat species from Chinese provinces. *J. Virol.* 86:10999–1012

55. Yinda CK, Ghogomu SM, Conceição-Neto N, Beller L, Deboutte W, et al. 2018. Cameroonian fruit bats harbor divergent viruses, including rotavirus H, bastroviruses, and picobirnaviruses using an alternative genetic code. *Virus Evol*. 4:vey008
56. Zheng XY, Qiu M, Guan WJ, Li JM, Chen SW, et al. 2018. Viral metagenomics of six bat species in close contact with humans in southern China. *Arch. Virol.* 163:73–88
57. Van Brussel K, Holmes EC. 2022. Zoonotic disease and virome diversity in bats. *Curr. Opin. Virol.* 52:192–202
58. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, et al. 2003. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 302:276–78
59. Tu C, Crameri G, Kong X, Chen J, Sun Y, et al. 2004. Antibodies to SARS coronavirus in civets. *Emerg. Infect. Dis.* 10:2244–48
60. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, et al. 2005. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *PNAS* 102:14040–45
61. Li W, Shi Z, Yu M, Ren W, Smith C, et al. 2005. Bats are natural reservoirs of SARS-like coronaviruses. *Science* 310:676–79
62. Yang X-L, Hu B, Wang B, Wang M-N, Zhang Q, et al. 2015. Isolation and characterization of a novel bat coronavirus closely related to the direct progenitor of severe acute respiratory syndrome coronavirus. *J. Virol.* 90:253–56
63. Tang XC, Zhang JX, Zhang SY, Wang P, Fan XH, et al. 2006. Prevalence and genetic diversity of coronaviruses in bats from China. *J. Virol.* 80:7481–90
64. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N. Engl. J. Med.* 367:1814–20
65. Sabir JSM, Lam TT-Y, Ahmed MMA, Li L, Shen Y, et al. 2016. Co-circulation of three camel coronavirus species and recombination of MERS-CoV in Saudi Arabia. *Science* 351:81–84
66. Anthony SJ, Gilardi K, Menachery VD, Goldstein T, Ssebide B, et al. 2017. Further evidence for bats as the evolutionary source of Middle East respiratory syndrome coronavirus. *mBio* 8:e00373-17
67. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, et al. 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 495:251–54
68. Yang Y, Du L, Liu C, Wang L, Ma C, et al. 2014. Receptor usage and cell entry of bat coronavirus HKU4 provide insight into bat-to-human transmission of MERS coronavirus. *PNAS* 111:12516–21
69. Ithete NL, Stoffberg S, Corman VM, Cottontail VM, Richards LR, et al. 2013. Close relative of human Middle East respiratory syndrome coronavirus in bat, South Africa. *Emerg. Infect. Dis.* 19:1697–99
70. Irving AT, Ahn M, Goh G, Anderson DE, Wang L-F. 2021. Lessons from the host defences of bats, a unique viral reservoir. *Nature* 589:363–70
71. Ruiz-Aravena M, McKee C, Gamble A, Lunn T, Morris A, et al. 2022. Ecology, evolution and spillover of coronaviruses from bats. *Nat. Rev. Microbiol.* 20:299–314
72. Banerjee A, Baker ML, Kulcsar K, Misra V, Plowright R, et al. 2020. Novel insights into immune systems of bats. *Front. Immunol.* 11:26
73. Zhou P, Tachedjian M, Wynne JW, Boyd V, Cui J, et al. 2016. Contraction of the type I IFN locus and unusual constitutive expression of IFN-α in bats. *PNAS* 113:2696–701
74. Anderson RM, May RM. 1991. *Infectious Diseases of Humans: Epidemiology and Control*. Oxford, UK: Oxford Univ. Press
75. Gibb R, Albery GF, Mollentze N, Eskew EA, Brierley L, et al. 2022. Mammal virus diversity estimates are unstable due to accelerating discovery effort. *Biol. Lett.* 18:20210427
76. Wille M, Geoghegan JL, Holmes EC. 2021. How accurately can we assess zoonotic risk? *PLOS Biol.* 19:e3001135
77. Hayman DTS, Knox MA. 2021. Estimating the age of the subfamily *Orthocoronavirinae* using host divergence times as calibration ages at two internal nodes. *Virology* 563:20–27
78. Gallaher WR. 2020. A palindromic RNA sequence as a common breakpoint contributor to copy-choice recombination in SARS-CoV-2. *Arch. Virol.* 165:2341–48
79. Boni MF, Lemey P, Jiang X, Lam TT, Perry BW, et al. 2020. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. *Nat. Microbiol.* 5:1408–17

80. Gorbalenya AE, Enjuanes L, Ziebuhr J, Snijder EJ. 2006. *Nidovirales*: evolving the largest RNA virus genome. *Virus Res.* 117:17–37
81. Sanjuán R, Domingo-Calap P. 2016. Mechanisms of viral mutation. *Cell. Mol. Life Sci.* 73:4433–48
82. Simon-Loriere E, Holmes EC. 2011. Why do RNA viruses recombine? *Nat. Rev. Microbiol.* 9:617–26
83. Geoghegan JL, Senior AM, Di Giallonardo F, Holmes EC. 2016. Virological factors that increase the transmissibility of emerging human viruses. *PNAS* 113:4170–75
84. Telenti A, Arvin A, Corti D, Diamond MS, García-Sastre A, et al. 2021. After the pandemic: perspectives on the future trajectory of COVID-19. *Nature* 596:495–504
85. Geoghegan JL, Holmes EC. 2018. The phylogenomics of evolving virus virulence. *Nat. Rev. Genet.* 19:756–69
86. Read AF. 1994. The evolution of virulence. *Trends Microbiol.* 2:73–76
87. Kerr PJ, Ghedin E, DePasse JV, Fitch A, Cattadori IM, et al. 2012. Evolutionary history and attenuation of myxoma virus on two continents. *PLOS Pathog.* 8:e1002950
88. Elsworth P, Cooke BD, Kovaliski J, Sinclair R, Holmes EC, Strive T. 2014. Increased virulence of Rabbit Haemorrhagic Disease Virus associated with genetic resistance in wild Australian rabbits (*Oryctolagus cuniculus*). *Virology* 464–465:415–23
89. Halfmann PJ, Iida S, Iwatsuki-Horimoto K, Maemura T, Kiso M, et al. 2022. SARS-CoV-2 Omicron virus causes attenuated disease in mice and hamsters. *Nature* 603:687–92
90. Meng B, Abdullahi A, Ferreira IATM, Goonawardane N, Saito A, et al. 2022. Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts tropism and fusogenicity. *Nature* 603:706–14
91. Shuai H, Chan JF, Hu B, Chai Y, Yuen TT, et al. 2022. Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. *Nature* 603:693–99
92. Horimoto T, Kawaoka Y. 2005. Influenza: lessons from past pandemics, warnings from current incidents. *Nat. Rev. Microbiol.* 3:591–600
93. Kelly TR, Karesh WB, Johnson CK, Gilardi KVK, Anthony SJ, et al. 2017. One Health proof of concept: bringing a transdisciplinary approach to surveillance for zoonotic viruses at the human-wild animal interface. *Prev. Vet. Med.* 137:112–18
94. Smith GJ, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, et al. 2009. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 459:1122–25
95. Shinde V, Bridges CB, Uyeki TM, Shu B, Balish A, et al. 2009. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N. Engl. J. Med.* 360:2616–25
96. Nelson MI, Gramer MR, Vincent AL, Holmes EC. 2012. Global transmission of influenza viruses from humans to swine, 2009–2011. *J. Gen. Virol.* 93:2195–203
97. Dobson A. 2004. Population dynamics of pathogens with multiple host species. *Am. Nat.* 164:S64–78
98. Holdo RM, Sinclair AR, Dobson AP, Metzger KL, Bolker BM, et al. 2009. A disease-mediated trophic cascade in the Serengeti and its implications for ecosystem C. *PLOS Biol.* 7:e1000210
99. Fountain-Jones NM, Kraberger S, Gagne RB, Gilbertson MLJ, Trumbo DR, et al. 2022. Hunting alters viral transmission and evolution in a large carnivore. *Nat. Ecol. Evol.* 6:174–82
100. Zinsstag J, Crump L, Schelling E, Hattendorf J, Maidane YO, et al. 2018. Climate change and One Health. *FEMS Microbiol. Lett.* 365:fny085
101. Morse SS. 1995. Factors in the emergence of infectious diseases. *Emerg. Infect. Dis.* 1:7–15
102. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, et al. 2017. Pathways to zoonotic spillover. *Nat. Rev. Microbiol.* 15:502–10
103. Campbell-Lendrum D, Manga L, Bagayoko M, Sommerfeld J. 2015. Climate change and vector-borne diseases: What are the implications for public health research and policy? *Philos. Trans. R. Soc. B* 370:20130552
104. Gould EA, Higgs S. 2009. Impact of climate change and other factors on emerging arbovirus diseases. *Trans. R. Soc. Trop. Med. Hyg.* 103:109–21
105. Tabachnick WJ. 2016. Climate change and the arboviruses: lessons from the evolution of the dengue and yellow fever viruses. *Annu. Rev. Virol.* 3:125–45
106. Haas SE, Hooten MB, Rizzo DM, Meentemeyer RK. 2011. Forest species diversity reduces disease risk in a generalist plant pathogen invasion. *Ecol. Lett.* 14:1108–16

107. Johnson PTJ, Preston DL, Hoverman JT, Richgels KLD. 2013. Biodiversity decreases disease through predictable changes in host community competence. *Nature* 494:230–33
108. Schmidt KA, Ostfeld RS. 2001. Biodiversity and the dilution effect in disease ecology. *Ecology* 82:609–19
109. Peng Y, Wu P, Schartup AT, Zhang Y. 2021. Plastic waste release caused by COVID-19 and its fate in the global ocean. *PNAS* 118:e2111530118
110. Shams M, Alam I, Mahbub MS. 2021. Plastic pollution during COVID-19: plastic waste directives and its long-term impact on the environment. *Environ. Adv.* 5:100119
111. Lu R, Zhao X, Li J, Niu P, Yang B, et al. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 395:565–74
112. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, et al. 2020. A new coronavirus associated with human respiratory disease in China. *Nature* 579:265–69
113. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579:270–73
114. Pekar J, Worobey M, Moshiri N, Scheffler K, Wertheim JO. 2021. Timing the SARS-CoV-2 index case in Hubei province. *Science* 372:412–17
115. Gianotti R, Barberis M, Fellegara G, Galván-Casas C, Gianotti E. 2021. COVID-19-related dermatosis in November 2019: Could this case be Italy's patient zero? *Br. J. Dermatol.* 184:970–71
116. Kong WH, Li Y, Peng MW, Kong DG, Yang XB, et al. 2020. SARS-CoV-2 detection in patients with influenza-like illness. *Nat. Microbiol.* 5:675–78
117. Shi M, Zhao S, Yu B, Wu W-C, Hu Y, et al. 2022. Total infectome characterization of respiratory infections in pre-COVID-19 Wuhan, China. *PLOS Pathog.* 18:e1010259
118. Worobey M. 2021. Dissecting the early COVID-19 cases in Wuhan. *Science* 374:1202–4
119. Holmes EC, Goldstein SA, Rasmussen AL, Robertson DL, Crits-Christoph A, et al. 2021. The origins of SARS-CoV-2: a critical review. *Cell* 184:4848–56
120. Xiao X, Newman C, Buesching CD, Macdonald DW, Zhou Z-M. 2021. Animal sales from Wuhan wet markets immediately prior to the COVID-19 pandemic. *Sci. Rep.* 11:11898
121. Freuling CM, Breithaupt A, Müller T, Sehl J, Balkema-Buschmann A, et al. 2020. Susceptibility of raccoon dogs for experimental SARS-CoV-2 infection. *Emerg. Infect. Dis.* 26:2982–85
122. Niu S, Wang J, Bai B, Wu L, Zheng A, et al. 2021. Molecular basis of cross-species ACE2 interactions with SARS-CoV-2-like viruses of pangolin origin. *EMBO J.* 40:e107786
123. Delaune D, Hul V, Karlsson EA, Hassanin A, Tey PO, et al. 2021. A novel SARS-CoV-2 related coronavirus in bats from Cambodia. *Nat. Commun.* 12:6563
124. Latinne A, Hu B, Olival KJ, Zhu G, Zhang L, et al. 2020. Origin and cross-species transmission of bat coronaviruses in China. *Nat. Commun.* 11:4235
125. Li LL, Wang JL, Ma XH, Sun XM, Li JS, et al. 2021. A novel SARS-CoV-2 related coronavirus with complex recombination isolated from bats in Yunnan province, China. *Emerg. Microbes Infect.* 10:1683–90
126. Murakami S, Kitamura T, Suzuki J, Sato R, Aoi T, et al. 2020. Detection and characterization of bat sarbecovirus phylogenetically related to SARS-CoV-2, Japan. *Emerg. Infect. Dis.* 26:3025–29
127. Temmam S, Vongphayloth K, Baquero E, Munier S, Bonomi M, et al. 2022. Bat coronaviruses related to SARS-CoV-2 and infectious for human cells. *Nature* 604:330–36
128. Wacharapluesadee S, Tan CW, Maneeorn P, Duengkae P, Zhu F, et al. 2021. Evidence for SARS-CoV-2 related coronaviruses circulating in bats and pangolins in Southeast Asia. *Nat. Commun.* 12:972
129. Zhou H, Chen X, Hu T, Li J, Song H, et al. 2020. A novel bat coronavirus closely related to SARS-CoV-2 contains natural insertions at the S1/S2 cleavage site of the spike protein. *Curr. Biol.* 30:2196–203
130. Zhou H, Ji J, Chen X, Bi Y, Li J, et al. 2021. Identification of novel bat coronaviruses sheds light on the evolutionary origins of SARS-CoV-2 and related viruses. *Cell* 184:4380–91
131. Lam TT-Y, Jia N, Zhang Y-W, Shum MH-H, Juan J-F, et al. 2020. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* 583:282–85
132. Gao W-H, Lin X-D, Chen Y-M, Xie C-G, Tan Z-Z, et al. 2020. Newly identified viral genomes in pangolins with fatal disease. *Virus Evol.* 6:veaa020
133. Holmes EC. 2022. COVID-19—lessons for zoonotic disease. *Science* 375:1114–15
134. Xu GJ, Kula T, Xu Q, Li MZ, Vernon SD, et al. 2015. Comprehensive serological profiling of human populations using a synthetic human virome. *Science* 348:aaa0698

135. Holmes EC, Rambaut A, Andersen KG. 2018. Pandemics: spend on surveillance, not prediction. *Nature* 558:180–82
136. Hilderink MH, de Winter II. 2021. No need to beat around the bushmeat—the role of wildlife trade and conservation initiatives in the emergence of zoonotic diseases. *Heliyon* 7:e07692
137. Karesh WB, Noble E. 2009. The bushmeat trade: increased opportunities for transmission of zoonotic disease. *Mt. Sinai J. Med.* 76:429–34
138. Carbis Bay G7 Summit Commun. 2021. *Our shared agenda for global action to build back better*. **https://www.consilium.europa.eu/media/50361/carbis-bay-g7-summit-communique.pdf**
139. Sokolow SH, Nova N, Pepin KM, Peel AJ, Pulliam JRC, et al. 2019. Ecological interventions to prevent and manage zoonotic pathogen spillover. *Philos. Trans. R. Soc. B* 374:20180342
140. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, et al. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220:868–71
141. Hahn BH, Shaw GM, de Cock KM, Sharp PM. 2000. AIDS as a zoonosis: scientific and public health implications. *Science* 287:607–14
142. Sharp PM, Hahn BH. 2011. Origins of HIV and the AIDS pandemic. *Cold Spring Harb. Perspect. Med.* 1:a006841