Cross-Species Transmission of Emerging Coronaviruses in Humans and Domestic Mammals

Nicole Nova[1*]

[1]Department of Biology, Stanford University, Stanford, CA, USA

*** Correspondence:**
Nicole Nova
nicole.nova@stanford.edu

Keywords: Coronavirus, COVID-19, cross-species transmission, host range, MERS, One Health, SARS, spillover.

Abstract

Coronaviruses cause respiratory and digestive diseases in vertebrates. The recent pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2, is taking a heavy toll on society and planetary health, and illustrates the threat emerging coronaviruses can pose to the well-being of humans and other animals. Coronaviruses are constantly evolving, crossing host species barriers, and expanding their host range. In the last few decades, several novel coronaviruses have emerged in humans and domestic animals. Novel coronaviruses have also been discovered in captive wildlife or wild populations, raising conservation concerns. The evolution and emergence of novel viruses is enabled by frequent cross-species transmission. It is thus crucial to determine emerging coronaviruses' potential for infecting different host species, and to identify the circumstances under which cross-species transmission occurs in order to mitigate the rate of disease emergence. Here, I review (broadly across several mammalian host species) up-to-date knowledge of host range and circumstances concerning reported cross-species transmission events of emerging coronaviruses in humans and common domestic mammals. All of these coronaviruses had similar host ranges, were closely related (indicative of rapid diversification and spread), and their emergence was likely associated with high-host-density environments facilitating multi-species interactions (e.g., shelters, farms, markets) and the health or well-being of animals as end- and/or intermediate spillover hosts. Further research is needed to identify mechanisms of the cross-species transmission events that have ultimately led to a surge of emerging coronaviruses in multiple species in a relatively short period of time in a world undergoing rapid environmental change.

1 Introduction

Coronaviruses (CoVs) cause respiratory and digestive diseases in humans and other animals, and are responsible for several emerging diseases. The severe acute respiratory syndrome (SARS) outbreak in 2002–2003 resulted in 8422 human cases and 916 deaths in 33 countries (1). In 2012, Middle East respiratory syndrome (MERS) emerged, and over time has resulted in over 2,500 human cases and 866 deaths in 27 countries (2,3). To date, the current novel coronavirus disease 2019 (COVID-19) pandemic has claimed 3.4 million human deaths and 164 million cases in 219 countries and territories (4). Other animals have also been affected by these and other emerging coronaviruses, all of which resulted from cross-species transmission, and demonstrate the serious threat coronaviruses can pose to humans and other animals globally.

Named after their crown-shaped spike surface proteins, coronaviruses are enveloped, positive-sense single-stranded RNA viruses that belong to the family *Coronaviridae*, subfamily *Orthocoronavirinae* (5,6). They split into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus* (5). The first two genera infect primarily mammals, whereas *Gammacoronaviruses* infect birds, and *Deltacoronaviruses* infect both mammals and birds (7). Coronaviruses further split into species; however, they exist as quasispecies due to the rapid evolution driven by their high mutation rates and homologous RNA recombination (8). Coronaviruses have the largest genomes (26.4–31.7 kilobases) of all known RNA viruses; thus, their genomes are extra prone to accumulation of mutations and recombined segments over time, which contributes to their diverse host range and potential for disease emergence (9).

Bats are considered reservoirs for most *Alpha-* and *Betacoronaviruses*, while wild birds are probable reservoirs for *Gamma-* and *Deltacoronaviruses* (10). Coronavirus spillover from reservoirs to other species, and subsequent cross-species transmission, is primarily mediated by recombination in the receptor-binding domain (RBD) of the spike protein (S) gene (11). RBD enables coronaviruses to infect hosts by binding to a host receptor, e.g., angiotensin-converting enzyme 2 (ACE2) in the case of SARS coronaviruses, for cell entry (7,12,13). Although research has revealed reservoirs and molecular mechanisms enabling cross-species transmission, and that viral evolution is facilitated by frequent cross-species transmission events (14), less is known about the environments favoring emerging coronavirus evolution in non-reservoir hosts.

Agriculture and industrialization expanded the global abundance of humans and domestic mammals (i.e., livestock and pets). Today, their combined biomass makes up 96% of all mammalian biomass on Earth (15). This may be the primary reason for disease emergence in humans and other animals (16). To help curb coronavirus disease emergence, it is important to identify current host ranges of existing coronaviruses in humans and domestic animals, and the circumstances associated with their cross-species transmission.

This review aims to provide an updated succinct summary of known host ranges and cross-species transmissions of recently emerged coronaviruses in humans and domestic mammals. Finally, I discuss commonalities among the circumstances related to spillover and emergence of several coronaviruses in various mammalian hosts, and how these may inform One Health interventions for preventing disease emergence.

2 Emerging human coronaviruses

There are seven known human coronaviruses: the *Betacoronaviruses* SARS-CoV-1, MERS-CoV, and SARS-CoV-2, which caused SARS, MERS, and COVID-19, respectively, and the

Alphacoronaviruses NL63 and 229E and *Betacoronaviruses* OC43 and HKU1, which cause the common cold in humans (17). The latter four may not be labeled as recently emerging coronaviruses, although they have spilled over at some point in the past. Bats are considered reservoirs for NL63 and 229E, whereas rodents are putative reservoirs for OC43 and HKU1 (17–19). NL63 possibly emerged several hundred years ago from recombination between ancestors to 229E in hipposiderid bats and coronaviruses circulating in African trident bats (19,20). Based on phylogenetic analyses, cattle and camelids have been identified as probable intermediate spillover hosts for OC43 and 229E emergence one and two centuries ago, respectively (17,18,20). The bovine-to-human spillover that led to OC43 emergence likely coincided with a pandemic in 1890 (17,21,22). Indeed, OC43 and bovine coronavirus share 96% global nucleotide identity (23). Finally, extant lineages of HKU1 trace their most recent common ancestor to the 1950s, when it possibly spilled over from rodents (20).

Next, this section covers plausible spillover events—from reservoirs to humans via potential intermediate host species—that generated the recent SARS-CoV-1, MERS-CoV, and SARS-CoV-2, and their cross-species transmission potential.

2.1 SARS-CoV-1

SARS emerged in Guangdong, China in 2002 (1). Successful efforts curbed the SARS epidemic, and only a few cases occurred in 2003–2004 (24). There have been no known SARS-CoV-1-related cases since.

Based on genetic and epidemiologic investigations, the first SARS-CoV-1-infected individuals likely contracted the virus from masked palm civets or other wildlife in wet markets (24–27). Civet isolates revealed ongoing adaptation, suggesting that they were not reservoir hosts, but intermediate spillover hosts that contracted the virus from horseshoe bats (26–30). Substantial evidence confirms bats as SARS reservoirs (26,28,29,31,32).

Wildlife samples from a market in Shenzhen revealed that SARS-CoV-1 shared 99.8% nucleotide identity with isolates from civets and a raccoon dog, and that a ferret badger had seroconverted against SARS-CoV-1 (24,26). Initial human cases reported direct or indirect contact with these animals via handling, killing, meat serving, or residing near wet markets (33). Surveys showed that animal (especially civet) traders, although asymptomatic, had disproportionately high seroconversion against SARS-CoV-1, suggesting they have been exposed to SARS-CoV-related viruses for several years before the SARS epidemic (24,26). Intermediate spillover hosts were not necessarily required for the evolution of SARS-CoV-1, since a bat SARS-like coronavirus is able to bind to ACE2 in humans and civets for cell entry (34). Nonetheless, civets may have amplified the virus and brought it closer to humans (35).

Additional mammals are susceptible to SARS-CoV-1 infection. Cats, ferrets, guinea pigs, golden hamsters, common marmosets, grivets, cynomolgus and rhesus macaques can be infected under experimental inoculation, seroconvert, display similar pathological signs as humans, and the monkeys and guinea pigs usually display mild clinical signs, while cats and golden hamsters show no clinical signs (36–44). In two studies, inoculated ferrets only exhibited signs of lethargy (36,37). Furthermore, cats and ferrets can shed SARS-CoV-1 and transmit the virus within each species (36). Cats have also been naturally infected by SARS-CoV-1 in an apartment block where residents had SARS, suggesting possible human-to-cat transmission (36). Although swine are susceptible to SARS-CoV-1 both experimentally and naturally, viral replication in (and shedding from) swine is poor (45–47). Mice and poultry are not susceptible to SARS-CoV-1 infection (45,48,49). Thus, SARS-CoV-1 was not uniquely adapted to humans, yet likely restricted to mammals.

2.2 MERS-CoV

MERS cases are still being reported since it became endemic in the Arabian peninsula. MERS does sporadically spread to other parts of the world, although with limited human-to-human transmission (50,51). Most outbreaks originate from independent spillover events.

Bats are putative reservoirs for MERS, while dromedary camels and other camelids are intermediate spillover hosts (52–54). Although rare, camel-to-human transmission does occur (51,55). Infected camels shed MERS-CoV via bodily fluids, especially nasal secretions, and exhibit sneezing, coughing, fever, and loss of appetite (56,57). Camel care-takers or consumers of camel products are at risk of contracting MERS-CoV (51). People in direct or indirect contact with camels have disproportionately high seroconversion against MERS-CoV (58). Surveys from 2010–2013 in Saudi Arabia show that 90% of 310 and 74% of 203 camels were MERS-CoV seropositive (59,60). Historical seropositive samples and phylogenetic analyses suggest that MERS-like coronaviruses have been circulating in camels for at least a few decades before MERS recently emerged in humans (52,60–63). Camel markets with both live and dead animals are believed to serve as hotspots for MERS-CoV transmission (64).

MERS-CoV may infect additional species. Rhesus macaques, common marmosets, swine, llamas, rabbits, and alpacas haven been infected experimentally, and the monkeys developed mild-to-moderate and moderate-to-severe disease, respectively, swine and llamas displayed rhinorrhea, while rabbits and alpacas showed no clinical signs, although alpacas shed MERS-CoV and transmitted it within its species (65–68). A virological survey found MERS-CoV in sheep, goats, donkeys, and a cow, but not in buffaloes, mules, or horses (69). A serological study confirms that equids might not be susceptible to MERS-CoV infection, although *in vitro* inoculation suggests otherwise (70). However, in an experimental inoculation study, sheep and horses did not show evidence of viral replication or seroconversion (68). Mice, golden hamsters, ferrets, and poultry are not considered susceptible to MERS-CoV infection, mainly because of their low host receptor homology with that of the MERS-CoV-susceptible species (67,71).

2.3 SARS-CoV-2

The current COVID-19 pandemic originated in Wuhan, China in 2019 (72,73), although the origin of its pathogen, SARS-CoV-2, is still unclear. Its ancestor probably originated in bats, since SARS-CoV-2 is most closely related to the 2013 and 2019 isolates from horseshoe bats in Yunnan, China at the genome level, although not at the RBD level, suggesting neither might bind to human ACE2, and are thus not direct ancestors of SARS-CoV-2 (72,74,75).

Conversely, isolates (pangolin-CoVs) from smuggled and diseased pangolins in Guangdong (2018–2019) are closely related to SARS-CoV-2 in the RBD region (76–79). Molecular binding simulations show that S proteins of SARS-CoV-2 and pangolin-CoVs can potentially recognize ACE2 in both humans and pangolins, suggesting possible pangolin-to-human spillover (76,77). However, because pangolin-CoVs (including strains from Guangxi) are not the closest relatives to SARS-CoV-2 at the genome level, they are likely not direct ancestors of SARS-CoV-2 (76,78,79). Nevertheless, a 2019 pangolin-CoV isolate from Guangdong displayed high genome-wide similarity with both SARS-CoV-2 and SARS-CoV-2's closest relative (from bats), suggesting SARS-CoV-2 may have originated from recombination among coronaviruses present in bats and other wildlife (76,77,79,80).

Like SARS-CoV-1, SARS-CoV-2 infects species with high ACE2 homology. Cats, ferrets, golden hamsters, tree shrews, common marmosets, grivets, cynomolgus and rhesus macaques have been infected with SARS-CoV-2 experimentally, shed the virus, and displayed similar or milder clinical and pathological signs as humans, although cats may not show signs of disease (81–90). Conversely, dogs have low susceptibility to SARS-CoV-2, and show lack of clinical signs or dog-to-dog transmission, possibly due to their low levels of ACE2 in the respiratory tract (81,90–92). Yet, cat-to-cat, ferret-to-ferret, hamster-to-hamster, and bat-to-bat transmission of SARS-CoV-2 has been confirmed experimentally (81,89,90,93). However, mice, swine and poultry are not susceptible to SARS-CoV-2 infection (49,71,81).

Accumulating evidence supports naturally occurring human-to-cat SARS-CoV-2 transmission, such as multiple reports worldwide of SARS-CoV-2-positive cats from confirmed or suspected SARS-CoV-2-positive owners (94). Natural human-to-dog transmission may be possible, as was confirmed by seroconversion and SARS-CoV-2 presence in two out of 15 dogs in close contact with COVID-19 patients, where the viral sequences from each dog-and-owner pair were identical (91). Serological and virological surveys conducted several months after the pandemic started indicate that SARS-CoV-2 prevalence is much lower in pet and street cats and dogs than in humans, even if pet owners had suspected or confirmed SARS-CoV-2 infection (95–99). Thus, cats and dogs can get infected under natural conditions, but rarely. However, certain environments might amplify natural infections and cross-species transmission. Supported by epidemiolocal and phylogenetic studies, several countries reported suspected human-to-mink, subsequent mink-to-mink, and mink-to-human transmission of SARS-CoV-2 on fur farms (94,100–102). SARS-CoV-2 has also been transmitted to tigers, lions, and gorillas in zoos, raising concern for wildlife conservation (103).

3 Emerging coronaviruses in domestic mammals

Since the advent of agriculture (~8,000 BC), several spillover events led to the emergence of novel pathogens in humans and domesticated animals (16). Genetic analyses place the common ancestor to all known coronaviruses at around 8,000 BC, and those of each genus at around 2,400–3,300BC (10). Like humans, domestic mammals have been experiencing an increasing rate of novel coronavirus emergence, especially within the last century.

Bovine coronavirus (BCoV) likely emerged from rodent-CoVs around 1400 AD (17,104). BCoV is transmitted via the fecal–oral route, causing bloody diarrhea and respiratory infections in cattle (105–107). BCoV-like viruses have also been detected in other domestic and wild ruminants (105). BCoV can infect dogs experimentally, although subclinically (108). Turkeys show clinical signs of enteritis when infected with BCoV experimentally, but chickens are not susceptible (109). Equine-CoV, discovered in 1999, plausibly also descended from BCoV and causes enteritis in horses (110–112). Only one human case of a BCoV-like infection has ever been reported (113).

There are two dog coronaviruses: an *Alphacoronavirus* called canine enteric coronavirus (CCoV), transmitted fecal-orally, with serotypes CCoV-I and CCoV-II, and a *Betacoronavirus* called canine respiratory coronavirus (CRCoV), which causes kennel cough (114). CRCoV was discovered in 2003 from a kennel outbreak (115). It was later also detected in samples from 1996 (116). It is closely related to BCoV and HCoV-OC43, and genetic analyses suggest that CRCoV arose from a recent host-species shift of BCoV from bovine to canine hosts (115,117).

CCoV was first isolated from an outbreak in military dogs in 1971 (114). Initially, CCoV infections were believed to be restricted to the enteric tract causing mild diarrheal disease (118), but

an increasing number of lethal pantropic infections suggests that CCoV is responsible for an emerging infectious disease in canines (114). There are three proposed subtypes of CCoV-II: original CCoV-IIa, recombinant CCoV-IIb, and CCoV-IIc (114). The two biotypes of CCoV-IIa have different tissue tropism and pathogenicity: "classical" CCoV-IIa is restricted to the small intestine causing enteritis, but the emerging "pantropic" CCoV-IIa causes leukopenia and is often fatal (114,119). In 2019, an Asian pantropic CCoV-IIa strain was also isolated from a wolf in Italy (120), suggesting spillover to wildlife of imported strains (121). Cats and swine are also susceptible to CCoV (122–124).

There are six porcine coronaviruses: four *Alphacoronaviruses*, transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCoV), porcine epidemic diarrhoea virus (PEDV), and swine acute diarrhea syndrome coronavirus (SADS-CoV), one *Betacoronavirus*, porcine haemagglutinating encephalomyelitis virus (PHEV), and one *Deltacoronavirus*, porcine deltacoronavirus (PDCoV) (125). TGEV, PEDV, SADS-CoV and PDCoV cause severe enteritis that are fatal in piglets, PHEV causes digestive and/or neurological disease, and PRCoV causes mild respiratory disease (125).

TGEV, discovered in 1946 (126), likely emerged from CCoV-II (127), and its less virulent descendent PRCoV was identified in 1984 (128). PHEV, first described in 1957, likely descended from BCoV (125). PEDV emerged in the 1970s in Europe and Asia, likely from bat-CoVs, and was introduced in North America in 2013 after a new PEDV strain emerged in China in 2010 (129–132). A serological study indicates that PEDV subsequently spilled over from domestic to feral swine populations in the US (133). PDCoV was first detected in swine samples from 2009 in Hong Kong (10,130). In 2014, PDCoV caused the first-reported outbreaks in USA and South Korea (134,135). It was proposed that the virus' ancestor originated from recombination between sparrow-CoV and bulbul-CoV (136). PDCoV is most closely related to *Deltacoronaviruses* sampled from Asian leopard cats and ferret badgers in Guangdong and Guangxi markets (the first documented cases of *Deltacoronaviruses* in mammals) (137), suggesting that these species could have acted as intermediates for interspecies PDCoV spillover (138). In 2016, SADS outbreaks emerged in Guangdong with evidence strongly suggesting bat-to-swine spillover origin (139).

There is one coronavirus that primarily infects cats: feline coronavirus (FCoV). This *Alphacoronavirus* exists in two serotypes: FCoV-I and FCoV-II (140). Both cause digestive diseases and are transmitted fecal-orally. FCoV-I is the most common type, but less virulent than FCoV-II (141,142). Comparative sequence studies indicate FCoV-I is genetically similar to CCoV-I, and FCoV-II emerged from recombination between FCoV-I and CCoV-II (119,140,143,144). Conceivably, FCoV-I and CCoV-I evolved from a common ancestor, while CCoV-II and FCoV-II arose as more virulent recombinants (127). For each serotype, there are two biotypes with different pathogenicity: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV). FECV usually causes mild diarrhea, whereas FIP is lethal. FIPV evolves from FECV via within-host mutations in the S gene that alter cell tropism, and emerges during persistent infection of FECV (140,145). In 2004, a disease resembling FIP was also discovered in ferrets caused by an emerging ferret systemic coronavirus, a decade after the first and less virulent ferret coronavirus (enteric) was discovered (146). FIP likely emerged in the 1950s, within a decade after the first TGE cases in swine in USA (126,147). Thus, FCoV is closely related to TGEV and CCoV, and recombinants among all three have emerged (148–150), probably because all three can cross-infect cats, swine, and dogs (123,149,151–153).

4 Discussion

Coronaviruses in humans and domestic animals are closely related (Figure), emerged recently and at an increasing rate. The circumstances associated with their emergence are high-animal-density environments that favor inter-species interactions (e.g., kennels, shelters, agricultural farms, fur farms, wet markets), which increase disease prevalence and promote cross-species transmission. Indeed, studies show that seroprevalence of CCoV is higher in kennels compared to the rest of the dog population, and shelters co-housing dogs with cats harbor recombinant canine-feline coronaviruses (114,149,151,154). Further, commercial agriculture have led to large numbers of domestic animals living in close proximity to humans, possibly driving the emergence of OC43 from cattle and MERS from camels.

Additionally, animals kept under detrimental conditions or exposed to stress (e.g., during transport) suffer from poor health and suppressed immune systems, rendering them more susceptible to infections (64,155). For example, mink fur farms, where animals are usually kept in small, unhygienic enclosures, generated new strains of SARS-CoV-2 causing secondary zoonoses (94,100–102). The wildlife trade and wet markets are conducive to disease emergence as well, since animals are transported and kept in small, unhygienic cages next to many different animal species (155). Indeed, a study showed that civets in markets were disproportionately positive for SARS-CoV-1 compared to civets on the supplying farms (30). Further, SARS-CoV-1 isolates from a civet and a racoon dog at the same market, but from different regions of China, had an identical S-gene sequence, which differed from that of the other civet isolates, indicating the occurrence of cross-species transmission at the market (26). Accordingly, the concept of One Health is important for suppressing coronavirus emergence.

Little is still known about host ranges and cross-species transmissions of coronaviruses. Most studies on this topic have been motivated by finding appropriate animal models for vaccine development, or identifying potential host species enabling viral persistence. However, future studies should expand their surveys beyond domestic, captive or common laboratory animals for a fuller comprehension of coronavirus emergence and the extent of its radiation (Figure). Surveillance efforts of coronaviruses in the wild are underway (e.g., PREDICT, Global Virome Project), which are important for identifying new coronaviruses with zoonotic potential, tracking spillover pathways, and potentially filling in the host range gaps of known coronaviruses in humans and domestic mammals (156,157).

Concurrently with the global expansion of humans and domestic mammals, various coronaviruses have emerged as a result of cross-species transmission among humans, domestic, and wild animals. Conceivably, the human and domestic mammal population increase: yielded a large enough susceptible population to maintain coronavirus circulation, provided more opportunities for novel coronavirus emergence via spillover among different species, and brought humans and domestic animals in closer contact with wild reservoirs (158–160). The mechanisms governing the surge and radiation of these recently emerged coronaviruses require further investigation. Actions reducing people’s dependency on domestic animals and demand for animal products, while improving the health of the animals remaining in captivity, may mitigate coronavirus emergence.

5 Conflict of Interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Author Contributions

NN performed the literature review and wrote the manuscript.

7 Funding

NN was supported by the Philanthropic Educational Organization (P.E.O.) Scholar Award from the International Chapter of the P.E.O. Sisterhood, the Environmental Venture Project Grant from the Stanford Woods Institute for the Environment, the Stanford Data Science Scholars program, and the Department of Biology at Stanford University.

8 Acknowledgments

I thank Tejas Athni, Alex Becker, Marissa Childs, Lisa Couper, Isabel Delwel, Johannah Farner, Caroline Glidden, Mallory Harris, Isabel Jones, Morgan Kain, Devin Kirk, Christopher LeBoa, Andrea Lund, Erin Mordecai, Maike Morrison, Eloise Skinner, Susanne Sokolow, and Krti Tallam for helpful feedback and discussion on this topic.

9 References

1. da Silva PG, Mesquita JR, de São José Nascimento M, Ferreira VAM. Viral, host and environmental factors that favor anthropozoonotic spillover of coronaviruses: An opinionated review, focusing on SARS-CoV, MERS-CoV and SARS-CoV-2. *Sci Total Environ* (2020) **750**:141483. doi:10.1016/j.scitotenv.2020.141483

2. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* (2012) **367**:1814–1820. doi:10.1056/NEJMoa1211721

3. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, Fouchier RAM, Galiano M, Gorbalenya AE, Memish ZA, et al. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group. *J Virol* (2013) **87**:7790–7792. doi:10.1128/jvi.01244-13

4. CNN Health. World Covid-19 tracker: Latest cases and deaths by country. (2021) Available at: https://www.cnn.com/interactive/2020/health/coronavirus-maps-and-cases/ [Accessed January 10, 2021]

5. de Groot RJ, Baker SC, Baric R, Enjuanes L, Gorbalenya AE, Holmes KV, Perlman S, Poon L, Rottier PJM, Talbot PJ, et al. "Family Coronaviridae," in *Virus Taxonomy Ninth Report ofthe International Committee on Taxonomy of Viruses*, eds. A. M. Q. King, M. J. Adams, E. B. Carstens, E. J. Lefkowitz (San Diego, CA: Elsevier Academic Press), 806–828. doi:10.1016/B978-0-12-384684-6.00068-9

6. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19

Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. *J Clin Med* (2020) **9**:1225. doi:10.3390/jcm9041225

7. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annu Rev Virol* (2016) **3**:237–261. doi:10.1146/annurev-virology-110615-042301

8. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses: An RNA proofreading machine regulates replication fidelity and diversity. *RNA Biol* (2011) **8**:270–279. doi:10.4161/rna.8.2.15013

9. Woo PCY, Huang Y, Lau SKP, Yuen KY. Coronavirus genomics and bioinformatics analysis. *Viruses* (2010) **2**:1805–1820. doi:10.3390/v2081803

10. Woo PCY, Lau SKP, Lam CSF, Lau CCY, Tsang AKL, Lau JHN, Bai R, Teng JLL, Tsang CCC, Wang M, et al. Discovery of Seven Novel Mammalian and Avian Coronaviruses in the Genus Deltacoronavirus Supports Bat Coronaviruses as the Gene Source of Alphacoronavirus and Betacoronavirus and Avian Coronaviruses as the Gene Source of Gammacoronavirus and Deltacoronavi. *J Virol* (2012) **86**:3995–4008. doi:10.1128/jvi.06540-11

11. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GF. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. *Trends Microbiol* (2016) **24**:490–502. doi:10.1016/j.tim.2016.03.003

12. Li W, Moore MJ, Vasllieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greeneugh TC, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* (2003) **426**:450–454. doi:10.1038/nature02145

13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* (2020) **181**:271-280.e8. doi:10.1016/j.cell.2020.02.052

14. Geoghegan JL, Duchêne S, Holmes EC. Comparative analysis estimates the relative frequencies of co-divergence and cross-species transmission within viral families. *PLoS Pathog* (2017) **13**:e1006215. doi:10.1371/journal.ppat.1006215

15. Bar-On YM, Phillips R, Milo R. The biomass distribution on Earth. *Proc Natl Acad Sci U S A* (2018) **115**:6506–6511. doi:10.1073/pnas.1711842115

16. Harper KN, Armelagos GJ. Genomics, the origins of agriculture, and our changing microbe-scape: time to revisit some old tales and tell some new ones. *Am J Phys Anthropol* (2013) **152 Suppl**:135–152. doi:10.1002/ajpa.22396

17. Corman VM, Muth D, Niemeyer D, Drosten C. "Hosts and Sources of Endemic Human Coronaviruses," in *Advances in Virus Research* (Academic Press Inc.), 163–188. doi:10.1016/bs.aivir.2018.01.001

18. Corman VM, Baldwin HJ, Tateno AF, Zerbinati RM, Annan A, Owusu M, Nkrumah EE, Maganga GD, Oppong S, Adu-Sarkodie Y, et al. Evidence for an Ancestral Association of Human Coronavirus 229E with Bats. *J Virol* (2015) **89**:11858–11870. doi:10.1128/jvi.01755-

15

19. Tao Y, Shi M, Chommanard C, Queen K, Zhang J, Markotter W, Kuzmin I V., Holmes EC, Tong S. Surveillance of Bat Coronaviruses in Kenya Identifies Relatives of Human Coronaviruses NL63 and 229E and Their Recombination History. *J Virol* (2017) **91**: doi:10.1128/jvi.01953-16

20. Forni D, Cagliani R, Clerici M, Sironi M. Molecular Evolution of Human Coronavirus Genomes. *Trends Microbiol* (2017) **25**:35–48. doi:10.1016/j.tim.2016.09.001

21. Vijgen L, Keyaerts E, Lemey P, Maes P, Van Reeth K, Nauwynck H, Pensaert M, Van Ranst M. Evolutionary History of the Closely Related Group 2 Coronaviruses: Porcine Hemagglutinating Encephalomyelitis Virus, Bovine Coronavirus, and Human Coronavirus OC43. *J Virol* (2006) **80**:7270–7274. doi:10.1128/jvi.02675-05

22. Vijgen L, Keyaerts E, Moës E, Thoelen I, Wollants E, Lemey P, Vandamme A-M, Van Ranst M. Complete Genomic Sequence of Human Coronavirus OC43: Molecular Clock Analysis Suggests a Relatively Recent Zoonotic Coronavirus Transmission Event. *J Virol* (2005) **79**:1595–1604. doi:10.1128/jvi.79.3.1595-1604.2005

23. Kin N, Miszczak F, Diancourt L, Caro V, Moutou F, Vabret A, Ar Gouilh M. Comparative molecular epidemiology of two closely related coronaviruses, bovine coronavirus (BCoV) and human coronavirus OC43 (HCoV-OC43), reveals a different evolutionary pattern. *Infect Genet Evol* (2016) **40**:186–191. doi:10.1016/j.meegid.2016.03.006

24. Wang LF, Eaton BT. Bats, civets and the emergence of SARS. *Curr Top Microbiol Immunol* (2007) **315**:325–344. doi:10.1007/978-3-540-70962-6_13

25. Wang M, Yan M, Xu H, Liang W, Kan B, Zheng B, Chen H, Zheng H, Xu Y, Zhang E, et al. SARS-CoV infection in a restaurant from palm civet. *Emerg Infect Dis* (2005) **11**:1860–1865. doi:10.3201/eid1112.041293

26. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China. *Science (80-)* (2003) **302**:276–278. doi:10.1126/science.1087139

27. Song HD, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. *Proc Natl Acad Sci U S A* (2005) **102**:2430–2435. doi:10.1073/pnas.0409608102

28. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, Wang H, Crameri G, Hu Z, Zhang H, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science (80-)* (2005) **310**:676–679. doi:10.1126/science.1118391

29. Yuan J, Hon CC, Li Y, Wang D, Xu G, Zhang H, Zhou P, Poon LLM, Lam TTY, Leung FCC, et al. Intraspecies diversity of SARS-like coronaviruses in Rhinolophus sinicus and its implications for the origin of SARS coronaviruses in humans. *J Gen Virol* (2010) **91**:1058–1062. doi:10.1099/vir.0.016378-0

30. Kan B, Wang M, Jing H, Xu H, Jiang X, Yan M, Liang W, Zheng H, Wan K, Liu Q, et al. Molecular Evolution Analysis and Geographic Investigation of Severe Acute Respiratory Syndrome Coronavirus-Like Virus in Palm Civets at an Animal Market and on Farms. *J Virol* (2005) **79**:11892–11900. doi:10.1128/jvi.79.18.11892-11900.2005

31. Lau SKP, Li KSM, Huang Y, Shek C-T, Tse H, Wang M, Choi GKY, Xu H, Lam CSF, Guo R, et al. Ecoepidemiology and Complete Genome Comparison of Different Strains of Severe Acute Respiratory Syndrome-Related Rhinolophus Bat Coronavirus in China Reveal Bats as a Reservoir for Acute, Self-Limiting Infection That Allows Recombination Events. *J Virol* (2010) **84**:2808–2819. doi:10.1128/jvi.02219-09

32. Lau SKP, Woo PCY, Li KSM, Huang Y, Tsoi HW, Wong BHL, Wong SSY, Leung SY, Chan KH, Yuen KY. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proc Natl Acad Sci U S A* (2005) **102**:14040–14045. doi:10.1073/pnas.0506735102

33. Xu RH, He JF, Evans MR, Peng GW, Field HE, Yu DW, Lee CK, Luo HM, Lin WS, Lin P, et al. Epidemiologic clues to SARS origin in China. *Emerg Infect Dis* (2004) **10**:1030–1037. doi:10.3201/eid1006.030852

34. Ge XY, Li JL, Yang X Lou, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* (2013) **503**:535–538. doi:10.1038/nature12711

35. Plowright RK, Eby P, Hudson PJ, Smith IL, Westcott D, Bryden WL, Middleton D, Reid PA, McFarlane RA, Martin G, et al. Ecological dynamics of emerging bat virus spillover. *Proc R Soc B Biol Sci* (2014) **282**:20142124. doi:10.1098/rspb.2014.2124

36. Martina BEE, Haagmans BL, Kuiken T, Fouchier RAM, Rimmelzwaan GF, Van Amerongen G, Peiris JSM, Lim W, Osterhaus ADME. SARS virus infection of cats and ferrets. *Nature* (2003) **425**:915. doi:10.1038/425915a

37. Van Den Brand JMA, L.haagmans B, Leijten L, Van Riel D, E.martina BE, Osterhaus ADME, Kuiken T. Pathology of experimental SARS coronavirus infection in cats and ferrets. *Vet Pathol* (2008) doi:10.1354/vp.45-4-551

38. Fouchier RAM, Kuiken T, Schutten M, Van Amerongen G, Van Doornum GJJ, Van Den Hoogen BG, Peiris M, Lim W, Stöhr K, Osterhaus ADME. Koch's postulates fulfilled for SARS virus. *Nature* (2003) **423**:240. doi:10.1038/423240a

39. Liang L, He C, Lei M, Li S, Hao Y, Zhu H, Duan Q. Pathology of guinea pigs experimentally infected with a novel reovirus and coronavirus isolated from SARS patients. *DNA Cell Biol* (2005) **24**:485–490. doi:10.1089/dna.2005.24.485

40. Roberts A, Vogel L, Guarner J, Hayes N, Murphy B, Zaki S, Subbarao K. Severe Acute Respiratory Syndrome Coronavirus Infection of Golden Syrian Hamsters. *J Virol* (2005) **79**:503–511. doi:10.1128/jvi.79.1.503-511.2005

41. Lawler J V, Endy TP, Hensley LE, Garrison A, Fritz EA, Lesar M, Baric RS, Kulesh DA, Norwood DA, Wasieloski LP, et al. Cynomolgus macaque as an animal model for severe acute respiratory syndrome. *PLoS Med* (2006) **3**:677–686. doi:10.1371/journal.pmed.0030149

42. Greenough TC, Carville A, Coderre J, Somasundaran M, Sullivan JL, Luzuriaga K, Mansfield K. Pneumonitis and multi-organ system disease in common marmosets (Callithrix jacchus) infected with the severe acute respiratory syndrome-associated coronavirus. *Am J Pathol* (2005) **167**:455–463. doi:10.1016/S0002-9440(10)62989-6

43. Rowe T, Gao G, Hogan RJ, Crystal RG, Voss TG, Grant RL, Bell P, Kobinger GP, Wivel NA, Wilson JM. Macaque Model for Severe Acute Respiratory Syndrome. *J Virol* (2004) **78**:11401–11404. doi:10.1128/jvi.78.20.11401-11404.2004

44. McAuliffe J, Vogel L, Roberts A, Fahle G, Fischer S, Shieh WJ, Butler E, Zaki S, St. Claire M, Murphy B, et al. Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. *Virology* (2004) **330**:8–15. doi:10.1016/j.virol.2004.09.030

45. Weingart HM, Copps J, Drebot MA, Marszal P, Smith G, Gren J, Andonova M, Pasick J, Kitching P, Czub M. Susceptibility of Pigs and Chickens to SARS Coronavirus. *Emerg Infect Dis* (2004) **10**:179–184. doi:10.3201/eid1002.030677

46. Wang M, Jing H qi, Xu H fang, Jiang X gao, Kan B, Liu Q yong, Wan K lin, Cui B yun, Zheng H, Cui Z gang, et al. Surveillance on severe acute respiratory syndrome associated coronavirus in animals at a live animal market of Guangzhou in 2004. *Zhonghua Liu Xing Bing Xue Za Zhi* (2005)

47. Chen W, Yan M, Yang L, Ding B, He B, Wang Y, Liu X, Liu C, Zhu H, You B, et al. SARS-associated coronavirus transmitted from human to pig. *Emerg Infect Dis* (2005) **11**:446–448. doi:10.3201/eid1103.040824

48. Swayne DE, Suarez DL, Spackman E, Tumpey TM, Beck JR, Erdman D, Rollin PE, Ksiazek TG. Domestic Poultry and SARS Coronavirus, Southern China. *Emerg Infect Dis* (2004) **10**:914–916. doi:10.3201/eid1005.030827

49. Yuan L, Tang Q, Cheng T, Xia N. Animal models for emerging coronavirus: progress and new insights. *Emerg Microbes Infect* (2020) **9**:949–961. doi:10.1080/22221751.2020.1764871

50. Gao H, Yao H, Yang S, Li L. From SARS to MERS: evidence and speculation. *Front Med* (2016) **10**:377–382. doi:10.1007/s11684-016-0466-7

51. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, Madani TA. Evidence for camel-to-human transmission of MERS coronavirus. *N Engl J Med* (2014) **370**:2499–2505. doi:10.1056/NEJMoa1401505

52. Müller MA, Corman VM, Jores J, Meyer B, Younan M, Liljander A, Bosch BJ, Lattwein E, Hilali M, Musa BE, et al. Mers coronavirus neutralizing antibodies in camels, eastern Africa, 1983–1997. *Emerg Infect Dis* (2014) **20**:2093–2095. doi:10.3201/eid2012.141026

53. Chu DKW, Poon LLM, Gomaa MM, Shehata MM, Perera RAPM, Zeid DA, El Rifay AS, Siu LY, Guan Y, Webby RJ, et al. MERS coronaviruses in dromedary camels, Egypt. *Emerg Infect Dis* (2014) **20**:1049–1053. doi:10.3201/eid2006.140299

54. Peck KM, Burch CL, Heise MT, Baric RS. Coronavirus Host Range Expansion and Middle

East Respiratory Syndrome Coronavirus Emergence: Biochemical Mechanisms and Evolutionary Perspectives. *Annu Rev Virol* (2015) **2**:95–117. doi:10.1146/annurev-virology-100114-055029

55. Hemida MG, Al-Naeem A, Perera RAPM, Chin AWH, Poon LLM, Peiris M. Lack of middle east respiratory syndrome coronavirus transmission from infected camels. *Emerg Infect Dis* (2015) **21**:699–701. doi:10.3201/eid2104.141949

56. Adney DR, van Doremalen N, Brown VR, Bushmaker T, Scott D, de Wit E, Bowen RA, Munster VJ. Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels. *Emerg Infect Dis* (2014) **20**:1999–2005. doi:10.3201/eid2012.141280

57. Hemida MG, Chu DKW, Poon LLM, Perera RAPM, Alhammadi MA, Ng HY, Siu LY, Guan Y, Alnaeem A, Peiris M. Mers coronavirus in dromedary camel herd, Saudi Arabia. *Emerg Infect Dis* (2014) **20**:1231–1234. doi:10.3201/eid2007.140571

58. Skariyachan S, Challapilli SB, Packirisamy S, Kumargowda ST, Sridhar VS. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for middle east respiratory syndrome coronavirus infections. *Front Microbiol* (2019) **10**:569. doi:10.3389/fmicb.2019.00569

59. Hemida MG, Perera RA, Wang P, Alhammadi MA, Siu LY, Li M, Poon LL, Saif L, Alnaeem A, Peiris M. Middle east respiratory syndrome (MERS) coronavirus seroprevalence in domestic livestock in Saudi Arabia, 2010 to 2013. *Eurosurveillance* (2013) **18**:20659. doi:10.2807/1560-7917.ES2013.18.50.20659

60. Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, de Wit E, Munster VJ, Hensley LE, Zalmout IS, Kapoor A, et al. Middle east respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. *MBio* (2014) **5**: doi:10.1128/mBio.00884-14

61. Sabir JSM, Lam TTY, Ahmed MMM, Li L, Shen Y, Abo-Aba SEM, Qureshi MI, Abu-Zeid M, Zhang Y, Khiyami MA, et al. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science (80-)* (2016) **351**:81–84. doi:10.1126/science.aac8608

62. Corman VM, Jores J, Meyer B, Younan M, Liljander A, Said MY, Gluecks I, Lattwein E, Bosch BJ, Drexler JF, et al. Antibodies against MERS coronavirus in dromedary camels, Kenya, 1992-2013. *Emerg Infect Dis* (2014) **20**:1319–1322. doi:10.3201/eid2008.140596

63. Lau SKP, Wong ACP, Lau TCK, Woo PCY. Molecular evolution of MERS coronavirus: Dromedaries as a recent intermediate host or long-time animal reservoir? *Int J Mol Sci* (2017) **18**:2138. doi:10.3390/ijms18102138

64. Hemida MG, Alnaeem A. Some One Health based control strategies for the Middle East respiratory syndrome coronavirus. *One Heal* (2019) **8**:100102. doi:10.1016/j.onehlt.2019.100102

65. Adney DR, Bielefeldt-Ohmann H, Hartwig AE, Bowen RA. Infection, replication, and transmission of Middle East respiratory syndrome coronavirus in alpacas. *Emerg Infect Dis* (2016) **22**:1031–1037. doi:10.3201/eid2206.160192

66. Crameri G, Durr PA, Klein R, Foord A, Yu M, Riddell S, Haining J, Johnson D, Hemida MG, Barr J, et al. Experimental infection and response to rechallenge of alpacas with middle east respiratory syndrome coronavirus. *Emerg Infect Dis* (2016) **22**:1071–1074. doi:10.3201/eid2206.160007

67. Van Doremalen N, Munster VJ. Animal models of Middle East respiratory syndrome coronavirus infection. *Antiviral Res* (2015) **122**:28–38. doi:10.1016/j.antiviral.2015.07.005

68. Vergara-Alert J, van den Brand JMA, Widagdo W, Muñoz M, Raj VS, Schipper D, Solanes D, Cordón I, Bensaid A, Haagmans BL, et al. Livestock susceptibility to infection with middle east respiratory syndrome coronavirus. *Emerg Infect Dis* (2017) **23**:232–240. doi:10.3201/eid2302.161239

69. Kandeil A, Gomaa M, Shehata M, El-Taweel A, Kayed AE, Abiadh A, Jrijer J, Moatasim Y, Kutkat O, Bagato O, et al. Middle East respiratory syndrome coronavirus infection in non-camelid domestic mammals. *Emerg Microbes Infect* (2019) **8**:103–108. doi:10.1080/22221751.2018.1560235

70. Meyer B, García-Bocanegra I, Wernery U, Wernery R, Sieberg A, Müller MA, Drexler JF, Drosten C, Eckerle I. Serologic assessment of possibility for MERS-CoV infection in equids. *Emerg Infect Dis* (2015) **21**:181–182. doi:10.3201/eid2101.141342

71. Suarez DL, Pantin-Jackwood MJ, Swayne DE, Lee SA, DeBlois SM, Spackman E. Lack of susceptibility to SARS-CoV-2 and MERS-CoV in Poultry. *Emerg Infect Dis* (2020) **26**:3074–3076. doi:10.3201/EID2612.202989

72. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020) **579**:270–273. doi:10.1038/s41586-020-2012-7

73. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, et al. A new coronavirus associated with human respiratory disease in China. *Nature* (2020) **579**:265–269. doi:10.1038/s41586-020-2008-3

74. Zhou H, Chen X, Hu T, Li J, Song H, Liu Y, Wang P, Liu D, Yang J, Holmes EC, et al. 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* (2020) **30**:2196-2203.e3. doi:10.1016/j.cub.2020.05.023

75. Latinne A, Hu B, Olival KJ, Zhu G, Zhang L, Li H, Chmura AA, Field HE, Zambrana-Torrelio C, Epstein JH, et al. Origin and cross-species transmission of bat coronaviruses in China. *Nat Commun* (2020) **11**:1–15. doi:10.1038/s41467-020-17687-3

76. Liu P, Jiang J-Z, Wan X-F, Hua Y, Li L, Zhou J, Wang X, Hou F, Chen J, Zou J, et al. Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)? *PLOS Pathog* (2020) **16**:e1008421. doi:10.1101/2020.02.18.954628

77. Xiao K, Zhai J, Feng Y, Zhou N, Zhang X, Zou JJ, Li N, Guo Y, Li X, Shen X, et al. Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. *Nature* (2020) **583**:286–289. doi:10.1038/s41586-020-2313-x

78. Lam TTY, Jia N, Zhang YW, Shum MHH, Jiang JF, Zhu HC, Tong YG, Shi YX, Ni XB, Liao YS, et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* (2020) **583**:282–285. doi:10.1038/s41586-020-2169-0

79. Zhang T, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. *Curr Biol* (2020) **30**:1346-1351.e2. doi:10.1016/j.cub.2020.03.022

80. Flores-Alanis A, Sandner-Miranda L, Delgado G, Cravioto A, Morales-Espinosa R. The receptor binding domain of SARS-CoV-2 spike protein is the result of an ancestral recombination between the bat-CoV RaTG13 and the pangolin-CoV MP789. *BMC Res Notes* (2020) **13**:398. doi:10.1186/s13104-020-05242-8

81. Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, Sun Z, et al. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. *Science (80-)* (2020) **368**:1016–1020. doi:10.1126/science.abb7015

82. Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Munnink BBO, De Meulder D, Van Amerongen G, Van Den Brand J, Okba NMA, et al. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. *Science (80-)* (2020) **368**:1012–1015. doi:10.1126/science.abb7314

83. Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Pérez-Pérez L, Schulz J, Meade-White K, Okumura A, Callison J, Brumbaugh B, et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. *Nature* (2020) **585**:268–272. doi:10.1038/s41586-020-2324-7

84. Woolsey C, Borisevich V, Prasad AN, Agans KN, Deer DJ, Dobias NS, Heymann JC, Foster SL, Levine CB, Medina L, et al. Establishment of an African green monkey model for COVID-19 and protection against re-infection. *Nat Immunol* (2021) **22**:86–98. doi:10.1038/s41590-020-00835-8

85. Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, Kaewpreedee P, Perera RAPM, Poon LLM, Nicholls JM, et al. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature* (2020) **583**:834–838. doi:10.1038/s41586-020-2342-5

86. Chan JFW, Zhang AJ, Yuan S, Poon VKM, Chan CCS, Lee ACY, Chan WM, Fan Z, Tsoi HW, Wen L, et al. Simulation of the Clinical and Pathological Manifestations of Coronavirus Disease 2019 (COVID-19) in a Golden Syrian Hamster Model: Implications for Disease Pathogenesis and Transmissibility. *Clin Infect Dis* (2020) **71**:2428–2446. doi:10.1093/cid/ciaa325

87. Zhao Y, Wang J, Kuang D, Xu J, Yang M, Ma C, Zhao S, Li J, Long H, Ding K, et al. Susceptibility of tree shrew to SARS-CoV-2 infection. *Sci Rep* (2020) **10**:16007. doi:10.1038/s41598-020-72563-w

88. Lu S, Zhao Y, Yu W, Yang Y, Gao J, Wang J, Kuang D, Yang M, Yang J, Ma C, et al. Comparison of nonhuman primates identified the suitable model for COVID-19. *Signal Transduct Target Ther* (2020) **5**:1–9. doi:10.1038/s41392-020-00269-6

89. Schlottau K, Rissmann M, Graaf A, Schön J, Sehl J, Wylezich C, Höper D, Mettenleiter TC, Balkema-Buschmann A, Harder T, et al. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens:

an experimental transmission study. *The Lancet Microbe* (2020) **1**:e218–e225. doi:10.1016/s2666-5247(20)30089-6

90. Bosco-Lauth AM, Hartwig AE, Porter SM, Gordy PW, Nehring M, Byas AD, VandeWoude S, Ragan IK, Maison RM, Bowen RA. Experimental infection of domestic dogs and cats with SARS-CoV-2: Pathogenesis, transmission, and response to reexposure in cats. *Proc Natl Acad Sci U S A* (2020) **117**:26382–26388. doi:10.1073/pnas.2013102117

91. Sit THC, Brackman CJ, Ip SM, Tam KWS, Law PYT, To EMW, Yu VYT, Sims LD, Tsang DNC, Chu DKW, et al. Infection of dogs with SARS-CoV-2. *Nature* (2020) **586**:776–778. doi:10.1038/s41586-020-2334-5

92. Zhai X, Sun J, Yan Z, Zhang J, Zhao J, Zhao Z, Gao Q, He W-T, Veit M, Su S. Comparison of Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein Binding to ACE2 Receptors from Human, Pets, Farm Animals, and Putative Intermediate Hosts. *J Virol* (2020) **94**: doi:10.1128/jvi.00831-20

93. Richard M, Kok A, de Meulder D, Bestebroer TM, Lamers MM, Okba NMA, Fentener van Vlissingen M, Rockx B, Haagmans BL, Koopmans MPG, et al. SARS-CoV-2 is transmitted via contact and via the air between ferrets. *Nat Commun* (2020) **11**:1–6. doi:10.1038/s41467-020-17367-2

94. Hosie MJ, Hofmann-Lehmann R, Hartmann K, Egberink H, Truyen U, Addie DD, Belák S, Boucraut-Baralon C, Frymus T, Lloret A, et al. Anthropogenic Infection of Cats during the 2020 COVID-19 Pandemic. *Viruses* (2021) **13**:185. doi:10.3390/v13020185

95. Sailleau C, Dumarest M, Vanhomwegen J, Delaplace M, Caro V, Kwasiborski A, Hourdel V, Chevaillier P, Barbarino A, Comtet L, et al. First detection and genome sequencing of SARS-CoV-2 in an infected cat in France. *Transbound Emerg Dis* (2020) **67**:2324–2328. doi:10.1111/tbed.13659

96. Temmam S, Barbarino A, Maso D, Behillil S, Enouf V, Huon C, Jaraud A, Chevallier L, Backovic M, Pérot P, et al. Absence of SARS-CoV-2 infection in cats and dogs in close contact with a cluster of COVID-19 patients in a veterinary campus. *One Heal* (2020) **10**:100164. doi:10.1016/j.onehlt.2020.100164

97. Chen J, Huang C, Zhang Y, Zhang S, Jin M. Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibodies in Pets in Wuhan, China. *J Clean Prod* (2020) **81**:e68–e69. doi:10.1016/j.jinf.2020.06.045

98. Zhang Q, Zhang H, Gao J, Huang K, Yang Y, Hui X, He X, Li C, Gong W, Zhang Y, et al. A serological survey of SARS-CoV-2 in cat in Wuhan. *Emerg Microbes Infect* (2020) **9**:2013–2019. doi:10.1080/22221751.2020.1817796

99. Deng J, Jin YY, Liu Y, Sun J, Hao L, Bai J, Huang T, Lin D, Jin YY, Tian K. Serological survey of SARS-CoV-2 for experimental, domestic, companion and wild animals excludes intermediate hosts of 35 different species of animals. *Transbound Emerg Dis* (2020) **67**:1745–1749. doi:10.1111/tbed.13577

100. Munnink BBO, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, Van

628 Der Spek A, Tolsma P, Rietveld A, Brouwer M, et al. Transmission of SARS-CoV-2 on mink
629 farms between humans and mink and back to humans. *Science (80-)* (2021) **371**:172–177.
630 doi:10.1126/science.abe5901

631 101. Costagliola A, Liguori G, Angelo D, Costa C, Ciani F, Giordano A. Do Animals Play a Role
632 in the Transmission of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)? A
633 Commentary. (2021) **2**:

634 102. Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Van Der Honing
635 RWH, Gerhards N, Tolsma P, Bouwstra R, Sikkema RS, et al. SARS-CoV-2 infection in
636 farmed minks, the Netherlands, April and May 2020. *Eurosurveillance* (2020) **25**:2001005.
637 doi:10.2807/1560-7917.ES.2020.25.23.2001005

638 103. Gibbons A. Captive gorillas test positive for coronavirus. *Science (80-)* (2021)
639 doi:10.1126/science.abg5458

640 104. Lau SKP, Woo PCY, Li KSM, Tsang AKL, Fan RYY, Luk HKH, Cai J-P, Chan K-H, Zheng
641 B-J, Wang M, et al. Discovery of a Novel Coronavirus, China Rattus Coronavirus HKU24,
642 from Norway Rats Supports the Murine Origin of Betacoronavirus 1 and Has Implications for
643 the Ancestor of Betacoronavirus Lineage A. *J Virol* (2015) **89**:3076–3092.
644 doi:10.1128/jvi.02420-14

645 105. Amer HM. Bovine-like coronaviruses in domestic and wild ruminants. *Anim Heal Res Rev*
646 (2019) **19**:113–124. doi:10.1017/S1466252318000117

647 106. Saif LJ. Bovine respiratory coronavirus. *Vet Clin North Am - Food Anim Pract* (2010) **26**:349–
648 364. doi:10.1016/j.cvfa.2010.04.005

649 107. Saif LJ, Redman DR, Moorhead PD, Theil KW. Experimentally induced coronavirus
650 infections in calves: viral replication in the respiratory and intestinal tracts. *Am J Vet Res*
651 (1986) **47**:1426–1432. Available at: https://pubmed.ncbi.nlm.nih.gov/3017160/ [Accessed
652 February 24, 2021]

653 108. Kaneshima T, Hohdatsu T, Hagino R, Hosoya S, Nojiri Y, Murata M, Takano T, Tanabe M,
654 Tsunemitsu H, Koyama H. The infectivity and pathogenicity of a group 2 bovine coronavirus
655 in pups. *J Vet Med Sci* (2007) **69**:301–303. doi:10.1292/jvms.69.301

656 109. Ismail MM, Cho KO, Ward LA, Saif LJ, Saif YM. Experimental bovine coronavirus in turkey
657 poults and young chickens. *Avian Dis* (2001) **45**:157–163. doi:10.2307/1593023

658 110. Pusterla N, Vin R, Leutenegger CM, Mittel LD, Divers TJ. Enteric coronavirus infection in
659 adult horses. *Vet J* (2018) **231**:13–18. doi:10.1016/j.tvjl.2017.11.004

660 111. Sanz MG, Kwon SY, Pusterla N, Gold JR, Bain F, Evermann J. Evaluation of equine
661 coronavirus fecal shedding among hospitalized horses. *J Vet Intern Med* (2019) **33**:918–922.
662 doi:10.1111/jvim.15449

663 112. Guy JS, Breslin JJ, Breuhaus B, Vivrette S, Smith LG. Characterization of a coronavirus
664 isolated from a diarrheic foal. *J Clin Microbiol* (2000) **38**:4523–4526.
665 doi:10.1128/jcm.38.12.4523-4526.2000

113. Zhang XM, Herbst W, Kousoulas KG, Storz J. Biological and genetic characterization of a hemagglutinating coronavirus isolated from a diarrhoeic child. *J Med Virol* (1994) **44**:152–161. doi:10.1002/jmv.1890440207

114. Licitra BN, Duhamel GE, Whittaker GR. Canine enteric coronaviruses: Emerging viral pathogens with distinct recombinant spike proteins. *Viruses* (2014) **6**:3363–3376. doi:10.3390/v6083363

115. Erles K, Toomey C, Brooks HW, Brownlie J. Detection of a group 2 coronavirus in dogs with canine infectious respiratory disease. *Virology* (2003) **310**:216–223. doi:10.1016/S0042-6822(03)00160-0

116. Ellis JA, McLean N, Hupaelo R, Haines DM. Detection of coronavirus in cases of tracheobronchitis in dogs: A retrospective study from 1971 to 2003. *Can Vet J* (2005)

117. Erles K, Shiu KB, Brownlie J. Isolation and sequence analysis of canine respiratory coronavirus. *Virus Res* (2007) **124**:78–87. doi:10.1016/j.virusres.2006.10.004

118. Tennant BJ, Gaskell RM, Kelly DF, Carter SD, Gaskell CJ. Canine coronavirus infection in the dog following oronasal inoculation. *Res Vet Sci* (1991) **51**:11–18. doi:10.1016/0034-5288(91)90023-H

119. Buonavoglia C, Decaro N, Martella V, Elia G, Campolo M, Desario C, Castagnaro M, Tempesta M. Canine coronavirus highly pathogenic for dogs. *Emerg Infect Dis* (2006) **12**:492–494. doi:10.3201/eid1203.050839

120. Alfano F, Dowgier G, Valentino MP, Galiero G, Tinelli A, Decaro N, Fusco G. Identification of pantropic canine coronavirus in a wolf (Canis lupus italicus) in Italy. *J Wildl Dis* (2019) **55**:504–508. doi:10.7589/2018-07-182

121. Alfano F, Fusco G, Mari V, Occhiogrosso L, Miletti G, Brunetti R, Galiero G, Desario C, Cirilli M, Decaro N. Circulation of pantropic canine coronavirus in autochthonous and imported dogs, Italy. *Transbound Emerg Dis* (2020) **67**:1991–1999. doi:10.1111/tbed.13542

122. McArdle F, Bennett M, Gaskell RM, Tennant B, Kelly DF, Gaskell CJ. Induction and enhancement of feline infectious peritonitis by canine coronavirus. *Am J Vet Res* (1992) **53**:1500–1506.

123. Woods RD, Cheville NF, Gallagher JE. Lesions in the small intestine of newborn pigs inoculated with porcine, feline, and canine coronaviruses. *Am J Vet Res* (1981) **42**:1163–1169. Available at: https://pubmed.ncbi.nlm.nih.gov/6168221/ [Accessed February 15, 2021]

124. Woods RD, Wesley RD. Seroconversion of pigs in contact with dogs exposed to canine coronavirus. *Can J Vet Res* (1992) **56**:78–80. Available at: /pmc/articles/PMC1263508/?report=abstract [Accessed February 15, 2021]

125. Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. *Vet Microbiol* (2020) **244**:108693. doi:10.1016/j.vetmic.2020.108693

126. Doyle LP, Hutchings LM. A transmissible gastroenteritis in pigs. *J Am Vet Med Assoc* (1946)

108:257–259. Available at: https://pubmed.ncbi.nlm.nih.gov/21020443/ [Accessed February 27, 2021]

127. Lorusso A, Decaro N, Schellen P, Rottier PJM, Buonavoglia C, Haijema B-J, de Groot RJ. Gain, Preservation, and Loss of a Group 1a Coronavirus Accessory Glycoprotein. *J Virol* (2008) **82**:10312–10317. doi:10.1128/jvi.01031-08

128. Pensaert M, Callebaut P, Vergote J. Isolation of a porcine respiratory, non-enteric coronavirus related to transmissible gastroenteritis. *Vet Q* (1986) **8**:257–261. doi:10.1080/01652176.1986.9694050

129. Decaro N, Martella V, Saif LJ, Buonavoglia C. COVID-19 from veterinary medicine and one health perspectives: What animal coronaviruses have taught us. *Res Vet Sci* (2020) **131**:21–23. doi:10.1016/j.rvsc.2020.04.009

130. Wang Q, Vlasova AN, Kenney SP, Saif LJ. Emerging and re-emerging coronaviruses in pigs. *Curr Opin Virol* (2019) **34**:39–49. doi:10.1016/j.coviro.2018.12.001

131. Huang YW, Dickerman AW, Piñeyro P, Li L, Fang L, Kiehne R, Opriessnig T, Meng XJ. Origin, evolution, and genotyping of emergent porcine epidemic diarrhea virus strains in the united states. *MBio* (2013) **4**:737–750. doi:10.1128/mBio.00737-13

132. Sun RQ, Cai RJ, Chen YQ, Liang PS, Chen DK, Song CX. Outbreak of porcine epidemic diarrhea in suckling piglets, China. *Emerg Infect Dis* (2012) **18**:161–163. doi:10.3201/eid1801.111259

133. Bevins SN, Lutman M, Pedersen K, Barrett N, Gidlewski T, Deliberto TJ, Franklin AB. Spillover of swine coronaviruses, United States. *Emerg Infect Dis* (2018) **24**:1390–1392. doi:10.3201/eid2407.172077

134. Wang L, Byrum B, Zhang Y. Detection and genetic characterization of deltacoronavirus in pigs, Ohio, USA, 2014. *Emerg Infect Dis* (2014) **20**:1227–1230. doi:10.3201/eid2007.140296

135. Lee S, Lee C. Complete genome characterization of Korean porcine deltacoronavirus strain KOR/KNU14-04/2014. *Genome Announc* (2014) **2**: doi:10.1128/genomeA.01191-14

136. Lau SKP, Wong EYM, Tsang C-C, Ahmed SS, Au-Yeung RKH, Yuen K-Y, Wernery U, Woo PCY. Discovery and Sequence Analysis of Four Deltacoronaviruses from Birds in the Middle East Reveal Interspecies Jumping with Recombination as a Potential Mechanism for Avian-to-Avian and Avian-to-Mammalian Transmission. *J Virol* (2018) **92**: doi:10.1128/jvi.00265-18

137. Dong BQ, Liu W, Fan XH, Vijaykrishna D, Tang XC, Gao F, Li LF, Li GJ, Zhang JX, Yang LQ, et al. Detection of a Novel and Highly Divergent Coronavirus from Asian Leopard Cats and Chinese Ferret Badgers in Southern China. *J Virol* (2007) **81**:6920–6926. doi:10.1128/jvi.00299-07

138. Ma Y, Zhang Y, Liang X, Lou F, Oglesbee M, Krakowka S, Li J. Origin, evolution, and virulence of porcine deltacoronaviruses in the United States. *MBio* (2015) **6**: doi:10.1128/mBio.00064-15

139. Zhou P, Fan H, Lan T, Yang X Lou, Shi WF, Zhang W, Zhu Y, Zhang YW, Xie QM, Mani S, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* (2018) **556**:255–259. doi:10.1038/s41586-018-0010-9

140. Tekes G, Thiel HJ. "Feline Coronaviruses: Pathogenesis of Feline Infectious Peritonitis," in *Advances in Virus Research* (Academic Press Inc.), 193–218. doi:10.1016/bs.aivir.2016.08.002

141. Lin CN, Chang RY, Su BL, Chueh LL. Full genome analysis of a novel type II feline coronavirus NTU156. *Virus Genes* (2013) **46**:316–322. doi:10.1007/s11262-012-0864-0

142. Wang YT, Su BL, Hsieh LE, Chueh LL. An outbreak of feline infectious peritonitis in a Taiwanese shelter: Epidemiologic and molecular evidence for horizontal transmission of a novel type II feline coronavirus. *Vet Res* (2013) **44**:57. doi:10.1186/1297-9716-44-57

143. Pratelli A, Martella V, Decaro N, Tinelli A, Camero M, Cirone F, Elia G, Cavalli A, Corrente M, Greco G, et al. Genetic diversity of a canine coronavirus detected in pups with diarrhoea in Italy. *J Virol Methods* (2003) **110**:9–17. doi:10.1016/S0166-0934(03)00081-8

144. Pratelli A, Martella V, Pistello M, Elia G, Decaro N, Buonavoglia D, Camero M, Tempesta M, Buonavoglia C. Identification of coronaviruses in dogs that segregate separately from the canine coronavirus genotype. *J Virol Methods* (2003) **107**:213–222. doi:10.1016/S0166-0934(02)00246-X

145. Rottier PJM, Nakamura K, Schellen P, Volders H, Haijema BJ. Acquisition of Macrophage Tropism during the Pathogenesis of Feline Infectious Peritonitis Is Determined by Mutations in the Feline Coronavirus Spike Protein. *J Virol* (2005) **79**:14122–14130. doi:10.1128/jvi.79.22.14122-14130.2005

146. Murray J, Kiupel M, Maes RK. Ferret coronavirus-associated diseases. *Vet Clin North Am - Exot Anim Pract* (2010) **13**:543–560. doi:10.1016/j.cvex.2010.05.010

147. Pedersen NC. A review of feline infectious peritonitis virus infection: 1963-2008. *J Feline Med Surg* (2009) **11**:225–258. doi:10.1016/j.jfms.2008.09.008

148. Herrewegh AAPM, Smeenk I, Horzinek MC, Rottier PJM, de Groot RJ. Feline Coronavirus Type II Strains 79-1683 and 79-1146 Originate from a Double Recombination between Feline Coronavirus Type I and Canine Coronavirus. *J Virol* (1998) **72**:4508–4514. doi:10.1128/jvi.72.5.4508-4514.1998

149. Benetka V, Kolodziejek J, Walk K, Rennhofer M, Möstl K. M gene analysis of atypical strains of feline and canine coronavirus circulating in an Austrian animal shelter. *Vet Rec* (2006) **159**:170–175. doi:10.1136/vr.159.6.170

150. Wesley RD. The S gene of canine coronavirus, strain UCD-1, is more closely related to the S gene of transmissible gastroenteritis virus than to that of feline infectious peritonitis virus. *Virus Res* (1999) **61**:145–152. doi:10.1016/S0168-1702(99)00032-5

151. Rennhofer M, Benetka V, Sommerfeld-Stur I, Möstl K. Epidemiological investigations on coronavirus infections in dogs and cats in an animal shelter. (2005).

152. Laber KE, Whary MT, Bingel SA, Goodrich JA, Smith AC, Swindle MM. "Biology and Diseases of Swine," in *Laboratory Animal Medicine* (Elsevier), 615–673. doi:10.1016/b978-012263951-7/50018-1

153. Saif L, Wesley R. "Transmissible gastroenteritis virus," in *Diseases of Swine*, eds. B. E. Straw, S. D'Allaire, W. L. Mengeling, D. J. Taylor (Ames, IA: Iowa State University Press).

154. Naylor MJ, Monckton RP, Lehrbach PR, Deane EM. Canine coronavirus in Australian dogs. *Aust Vet J* (2001) **79**:116–119. doi:10.1111/j.1751-0813.2001.tb10718.x

155. Baker SE, Cain R, Kesteren F Van, Zommers ZA, D'Cruze N, MacDonald DW. Rough trade: Animal welfare in the global wildlife trade. *Bioscience* (2013) **63**:928–938. doi:10.1525/bio.2013.63.12.6

156. Carlson CJ. From PREDICT to prevention, one pandemic later. *The Lancet Microbe* (2020) **1**:e6–e7. doi:10.1016/s2666-5247(20)30002-1

157. Global Virome Project. Available at: http://www.globalviromeproject.org/ [Accessed May 30, 2021]

158. Lorusso A, Calistri P, Petrini A, Savini G, Decaro N. Novel coronavirus (COVID-19) epidemic: a veterinary perspective. *Vet Ital* (2020)5–10. doi:10.12834/VetIt.2173.11599.1

159. Roche B, Garchitorena A, Guégan JF, Arnal A, Roiz D, Morand S, Zambrana-Torrelio C, Suzán G, Daszak P. Was the COVID-19 pandemic avoidable? A call for a "solution-oriented" approach in pathogen evolutionary ecology to prevent future outbreaks. *Ecol Lett* (2020) **23**:1557–1560. doi:10.1111/ele.13586

160. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, Lloyd-Smith JO. Pathways to zoonotic spillover. *Nat Rev Microbiol* (2017) **15**:502–510. doi:10.1038/nrmicro.2017.45

10 Figure

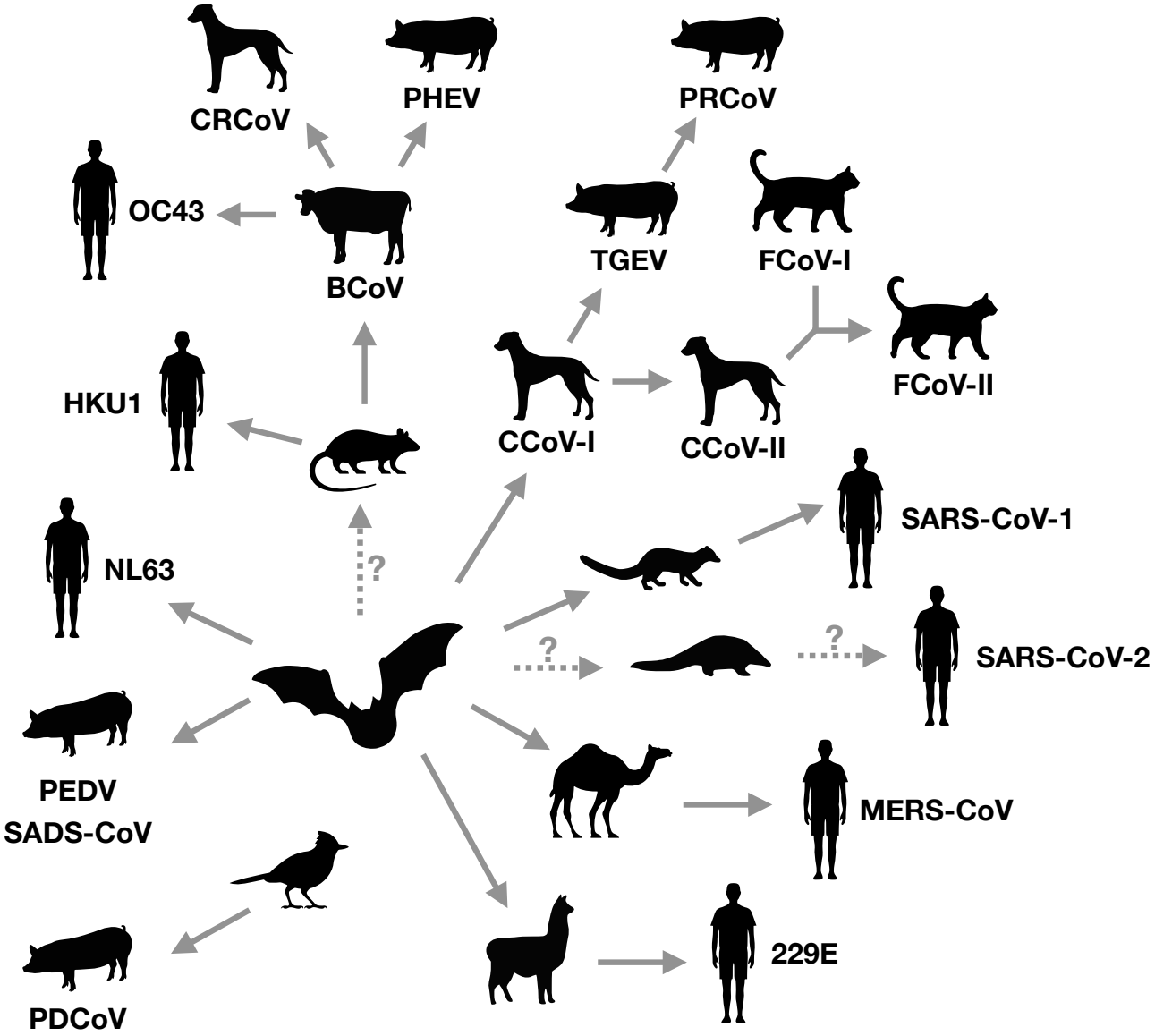

Figure. The evolution and radiation of coronaviruses in humans and common domestic mammals. Arrows indicate direction of spillover of coronavirus emergence (dashed arrows indicate less established spillover pathways). The radiation suggests there could be a vicious cycle of coronavirus emergence, whereby existing new viruses in new hosts increases the likelihood of producing more new recombinants.