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Overview

Coronaviruses: Troubling Crown of the Animal Kingdom

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The existence of coronaviruses has been known for many years. These viruses cause significant disease that primarily seems to affect agricultural species. Human coronavirus disease due to the 2002 outbreak of Severe Acute Respiratory Syndrome and the 2012 outbreak of Middle East Respiratory Syndrome made headlines; however, these outbreaks were controlled, and public concern quickly faded. This complacency ended in late 2019 when alarms were raised about a mysterious virus responsible for numerous illnesses and deaths in China. As we now know, this novel disease called Coronavirus Disease 2019 (COVID-19) was caused by *Severe acute respiratory syndrome-related-coronavirus*-2 (SARS-CoV-2) and rapidly became a worldwide pandemic. Luckily, decades of research into animal coronaviruses hastened our understanding of the genetics, structure, transmission, and pathogenesis of these viruses. Coronaviruses infect a wide range of wild and domestic animals, with significant economic impact in several agricultural species. Their large genome, low dependency on host cellular proteins, and frequent recombination allow coronaviruses to successfully cross species barriers and adapt to different hosts including humans. The study of the animal diseases provides an understanding of the virus biology and pathogenesis and has assisted in the rapid development of the SARS-CoV-2 vaccines. Here, we briefly review the classification, origin, etiology, transmission mechanisms, pathogenesis, clinical signs, diagnosis, treatment, and prevention strategies, including available vaccines, for coronaviruses that affect domestic, farm, laboratory, and wild animal species. We also briefly describe the coronaviruses that affect humans. Expanding our knowledge of this complex group of viruses will better prepare us to design strategies to prevent and/or minimize the impact of future coronavirus outbreaks.

Abbreviations: BCoV, Bovine coronavirus; CCoV, canine coronavirus; CoV(s), coronavirus(es); COVID-19, Coronavirus Disease 2019; CRCoV, canine respiratory coronavirus; E, Coronaviral envelope protein; ECoV, equine coronavirus; FCoV, feline coronavirus; FIPV, feline infectious peritonitis virus; GfCoV, guinea fowl coronavirus; HCoV, Human coronavirus; IBV, infectious bronchitis virus; M, Coronaviral membrane protein; MERS, Middle East Respiratory Syndrome-Coronavirus; MHV, mouse hepatitis virus; PEDV, porcine epidemic diarrhea virus; PDCoV, porcine deltacoronavirus; PhCoV, pheasant coronavirus; PHEV, porcine hemagglutinating encephalomyelitis virus; PRCoV, porcine respiratory coronavirus; RT-PCR, Reverse transcriptase polymerase chain reaction; S, Coronaviral spike protein; SADS-CoV, swine acute diarrhea syndrome-coronavirus; SARS-CoV, Severe Acute Respiratory Syndrome-Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome–Coronavirus–2; TCoV, turkey coronavirus; TGEV, transmissible gastroenteritis virus;

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Introduction

In the last 2 decades, 3 major Coronavirus (CoV) outbreaks, including the current Coronavirus Disease 2019 (COVID-19) pandemic, have affected hundreds of millions and killed millions of people. In all 3 outbreaks, the etiologic agents were novel coronaviruses (CoVs) that crossed species barriers and adapted to humans. CoVs infect a wide range of both wild and domestic species.[11] Their large genome size, the largest among RNA viruses, limited dependency on host cellular proteins, and frequent recombination allow CoVs to efficiently cross species.[174,278] In fact, all known human CoVs originated in animals.[257] Bats and birds are believed to be the ancestral hosts and natural reservoirs for all CoVs, with occasional transmission to other animals, including humans.[174,203,257,427,431] While the natural reservoir for the virus that causes COVID-19, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), has not been formally identified, the genome sequence of the virus is most closely related to bat coronaviruses.[335,397] In 1968, the name "coronavirus" was first proposed to describe this group of viruses based on their distinctive morphology by electron microscopy examination and other characteristics common to avian infectious bronchitis virus, mouse hepatitis virus, and human coronavirus strains.[184] In this review, we describe the CoVs, their origins, transmission mechanisms, pathogenesis, clinical signs, diagnosis, treatment, and prevention. Better understanding of this complex group of viruses should allow the development of strategies to prevent and/or minimize the impact of potential future outbreaks.

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Coronaviral Classification and General Information

The International Committee on Taxonomy of Viruses (ICTV) in its latest release (March 2021) classifies coronaviruses as members of the *Nidovirales* order, suborder *Cornidovirineae*, family *Coronaviridae*, subfamily *Orthocoronavirinae.* The relevant coronaviruses affecting animals are further subdivided into 4 genera, the *Alphacoronavirus* with 14 subgenera, the *Betacoronavirus* with 5 subgenera, the *Deltacoronavirus* with 3 subgenera, and the *Gammacoronavirus* with 3 subgenera (Figure 1).[206] Alpha- and betacoronaviruses infect mammals while delta- and gammacoronaviruses infect, with a few exceptions, mostly birds.[469]

All members of the Nidovirales order are enveloped, nonsegmented, positive-sense RNA viruses with genomes of around 30 kilobases. They possess a highly conserved genomic organization, express many nonstructural genes, have several unique enzymatic activities, and express downstream genes by synthesis of 3′ nested subgenomic mRNAs.[146] Coronavirus virions are spherical with diameters of approximately 125 nm, with the most prominent feature being club-shaped spike projections (peplomers) on the surface that resemble a solar corona (Latin *corona*, crown), leading to the name coronavirus.[22,333] The virion contains a helically symmetrical nucleocapsid that is not common in positive-sense RNA viruses.[146]

CoVs contain 4 main structural proteins (Figure 2): the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome.[146] The S protein, the main antigenic component against which neutralizing antibodies are created during natural infection, is cleaved by host cell proteases into 2 polypeptides, the S1 which constitutes the large receptor binding domain of the S protein, and the S2 which constitutes the stalk of the spike molecule.[1,113,292] S1 is responsible for viral attachment to specific host cell receptors, and S2 undergoes major conformational changes that lead to the fusion of the virion envelope and the host cell plasma membrane.[1,40,56,292,315] The M protein is the most abundant structural protein in the virion, essential for the morphogenesis process, and it is thought to give the virion its shape.[16] The M protein is a type III glycoprotein that directs most of the protein-protein interactions required for assembly of CoVs and binds to the nucleocapsid, promoting the completion of virion assembly. Glycosylation of the M protein affects organo-tropism and interferon (IFN) inducing capacity in some CoVs.[114,264] The E protein is found in small quantities in coronaviruses and is highly diverse, with its main function thought to be the assembly and release of the virus.[123] The E proteins from different CoVs are highly divergent but share a common architecture, have ion channel activity, facilitate assembly and release of the virus, and are required for pathogenesis.[68,337,390] The N protein is a highly basic phosphoprotein in the nucleocapsid and has 2 different domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both of which bind RNA.[246] In association with genomic viral RNA (gRNA), the N protein forms the helical nucleocapsid that is stabilized by binding to the M protein. The viral genome and helical nucleocapsid are surrounded by a host-derived lipid bilayer that anchors the S, E, and M proteins. In addition to its function in the virion, N protein also modulates viral RNA synthesis.[80,204,246,413,418,467] A fifth structural protein that is present only in a subset of betacoronaviruses in the subgenus *Embecovirus* is hemagglutinin-esterase (HE), which binds sialic acids on surface glycoproteins and contains acetyl-esterase activity that functions as a receptor-destroying enzyme, enhancing viral S protein-mediated mucosal cell invasion and spread.[100] In human CoVs OC43 and HKU1, HE-mediated receptor binding was selected against and ultimately lost through progressive accumulation of mutations in the HE lectin domain as an adaptation to the human upper respiratory tract.[18] Phylogenetic analysis suggests that the HE genes of CoVs and influenza C virus have a common ancestral origin, and that bovine coronaviruses and HCoV-OC43 are closely related.[506]

Viral cell attachment and invasion are initiated by the interaction of the S1 protein and its receptor binding domain (RBD) with the host cell receptors. Most alphacoronaviruses use aminopeptidase N as their host cellular receptor (that is, Canine Coronavirus, Feline Infectious Peritonitis Virus, Transmissible Gastroenteritis Virus, and Human Coronavirus-229E), while betacoronaviruses use the angiotensin-converting enzyme receptor (Severe Acute Respiratory Syndrome-Coronavirus and Severe Acute Respiratory Syndrome-Coronavirus-2), the dipeptidyl-peptidase 4 receptor (Middle East Respiratory Syndrome-Coronavirus), the *N*-acetyl-9-*O*-acetylneuraminic acid receptor (Bovine Coronavirus), the murine carcinoembryonic antigen-related cell adhesion molecule 1 receptor (Mouse Hepatitis Virus), and possibly others yet to be identified.[42,125,194,273,277,329,370,391,437,476,495,508]

Once the virus binds to the cell, fusion of the viral and cellular membranes occurs as a result of S protein cleavage exposing a fusion peptide that inserts into the cell membrane. Once the viral genome is released into the cytoplasm, translation of the replicase gene from the virion genomic RNA occurs by means of 2 large open reading frames (ORFs) that express 2 coterminal polyproteins.[21] These polyproteins contain nonstructural proteins whose main role is to assemble the replicase-transcriptase complex (RTC) to create an environment suitable for RNA synthesis; they are ultimately responsible for RNA replication and transcription of subgenomic RNAs that serve as mRNAs for the structural and accessory genes.[405,512] The accessory genes are coded by additional ORFs and are not essential for virus replication but are important in virus-host interactions including regulating innate immunity, viral proliferation, and pathogenicity.[144] Loss of accessory genes through spontaneous mutations, or reversed genetics, reduces virulence.[248] Nonstructural proteins (nsp) also have several functions related to viral cell invasion and can block host innate immune responses.[405,432] For example, nsp1 proteins from alpha- and beta-CoVs can suppress host gene expression and protein synthesis and can block innate immune responses by direct inhibition of translation or by promoting degradation of host IFN mRNA.[200,270,328,435,500] In addition, nsp3, nsp5, nsp8, nsp15, and nsp16 can, by different mechanisms, interfere with or block host innate immunity, contributing to immune evasion and facilitating viral infection.[83,244,309,375]

After replication and subgenomic RNA synthesis, the viral structural proteins S, E, and M are translated and inserted into the endoplasmic reticulum and follow the secretory pathway endoplasmic reticulum-Golgi intermediate compartment (ERGIC); there the viral genomes encapsidated by the N protein will bud into membranes of the ERGIC containing viral structural proteins, forming mature virions. Virions are then transported to the cell surface in vesicles and released by exocytosis.[241,436] In some coronaviruses, S protein that is not assembled into virions migrates to the cell surface where it mediates cell-cell fusion between infected and adjacent uninfected cells, leading to the formation of giant multinucleated cells (syncytia) and allowing the virus to spread by evading the host immune response.[146] Coronaviruses are well known for their ability to recombine using both homologous and nonhomologous recombination,

Family	Subfamily	Genus	Subgenus	Species
Coronaviridae	*Orthocoronavirinae*	*Alphacoronavirus*	*Colacovirus*	*Bat coronavirus CDPHE15*
			Decacovirus	*Bat coronavirus HKU10*
				Rhinolophus ferrumequinum alphacoronavirus HuB-2013
			Duvinacovirus	*Human coronavirus 229E*
			Luchacovirus	*Lucheng Rn rat coronavirus*
			Minacovirus	*Mink coronavirus 1*
			Minunacovirus	*Miniopterus bat coronavirus 1*
				Miniopterus bat coronavirus HKU8
			Myotacovirus	*Myotis ricketti alphacoronavirus Sax-2011*
			Nyctacovirus	*Nyctalus velutinus alphacoronavirus SC-2013*
				Pipistrellus kuhlii coronavirus 3398
			Pedacovirus	*Porcine epidemic diarrhea virus*
				Scotophilus bat coronavirus 512
			Rhinacovirus	*Rhinolophus bat coronavirus HKU2*
			Setracovirus	*Human coronavirus NL63*
				NL63-related bat coronavirus strain BtKYNL63-9b
			Soracovirus	*Sorex araneus coronavirus T14*
			Sunacovirus	*Suncus murinus coronavirus ×74*
			Tegacovirus	*Alphacoronavirus 1*
		Betacoronavirus	*Embecovirus*	*Betacoronavirus 1*
				China Rattus coronavirus HKU24
				Human coronavirus HKU1
				Murine coronavirus
				Myodes coronavirus 2JL14
			Hibecovirus	*Bat Hp-betacoronavirus Zhejiang2013*
			Merbecovirus	*Hedgehog coronavirus 1*
				Middle East respiratory syndrome-related coronavirus
				Pipistrellus bat coronavirus HKU5
				Tylonycteris bat coronavirus HKU4
			Nobecovirus	*Eidolon bat coronavirus C704*
				Rousettus bat coronavirus GCCDC1
				Rousettus bat coronavirus HKU9
			Sarbecovirus	*Severe acute respiratory syndrome-related coronavirus*
		Deltacoronavirus	*Andecovirus*	*Wigeon coronavirus HKU20*
			Buldecovirus	*Bulbul coronavirus HKU11*
				Common moorhen coronavirus HKU21
				Coronavirus HKU15
				Munia coronavirus HKU13
				White-eye coronavirus HKU16
			Herdecovirus	*Night heron coronavirus HKU19*
		Gammacoronavirus	*Brangacovirus*	*Goose coronavirus CB17*
			Cegacovirus	*Beluga whale coronavirus SW1*
			Igacovirus	*Avian coronavirus*
				Avian coronavirus 9203
				Duck coronavirus 2714

Figure 1. Coronavirus classification according to the International Committee on Taxonomy of Viruses. Adapted from reference 206.

which are thought to be important in viral evolution and adaptation to new hosts.[225,249,420] The viral replicase does not have a good proof-reading ability, incorporating incorrect nucleotides at each replication cycle and leading to accumulation of mutations in the viral genome; this results in the progressive differentiation of the viral progeny from the parental strain.[20,251]

Protein	Composition	Function
Spike (S)	Heavily glycosylated transmembrane protein cleaved by host cell proteases into S1 and S2.	S1 binds to host cell receptors. S2 mediates fusion of the virion envelope and host cell plasma membrane.
Membrane (M)	Type III glycoprotein.	Essential for virus assembly and thought to give the virion its shape.
Envelope (E)	Highly diverse transmembrane protein.	Facilitates assembly and release of the virus. Required for pathogenesis.
Nucleocapsid (N)	Heavily phosphorylated protein.	Binds RNA and forms the helical nucleocapsid. Modulates viral RNA synthesis.
Hemagglutinin-esterase (HE)[1]	Transmembrane glycoprotein with acetyl-esterase activity.	Binds sialic acids on surface glycoproteins. Enhances S protein-mediated cell entry and mucosal spread.

[1] Present only in a subset of betacoronaviruses.

Figure 2. Summary of Coronavirus structural proteins composition and function.

This characteristic replication of CoVs also allows recombination events during CoV coinfections; RNA polymerase from one strain can transfer to the RNA of the other strain to produce a hybrid RNA containing sequences from both viruses (a homologous recombination).[20,251] Recombination can also occur between a CoV and another RNA virus (heterologous recombination).[199,291] These mutations and recombination events may increase viral transmissibility and pathogenicity or support adaptation to a new host species.[20]

CoVs cause disease in many different species of mammals and birds. Clinical signs depend on the organs affected, which is determined by the S protein–receptor interaction between the virus and the host cell. Figure 3 summarizes salient features of the coronaviral infections. The majority of CoVs cause more severe disease in neonatal, young, or immunocompromised animals. In contrast, a few CoVs, most prominently ferret coronavirus, can cause severe disease in older ferrets while young ferrets often show mild disease.[475] Age susceptibility is relevant to determining the best age for vaccination. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most common method of diagnosis followed by serologic assays. Currently more than 80 USDA-licensed animal vaccines are available; however, their effectiveness is highly variable because natural mucosal infections usually do not provide immunity to prevent subsequent infections, and the propensity of the virus for recombination makes the vaccine less effective, or in some cases, the vaccine itself may lead to enhanced disease.[433,450,456] In addition, no effective or approved antiviral treatments are available for animal CoVs.

Human Coronaviruses

Seven different species of CoVs are known to cause disease in humans. Four of these viruses are well adapted to humans and found endemically across the globe; they cause seasonal, mild to moderate upper respiratory disease in temperate climates.[420,446] The other 3 can cause severe respiratory disease in humans, with SARS-CoV-2 being highly transmissible and currently prevalent across all continents.[107,146]

Human Coronavirus: HCoV-229E. *Human coronavirus (HCoV) 229E* belongs to the genus *Alphacoronavirus* (subgenus *Duvinacovirus*). In 1965, a previously unidentified virus was isolated in human embryonic tracheal organ culture of sample B814, a nasal swab and a washing sample from a boy with common cold symptoms.[441] The following year, a new virus was isolated from adult patients with common cold symptoms and was designated as strain 229E.[185] Other viruses similar to strain 229E were successfully cultured in human embryonic intestine cell cultures from patients with upper respiratory tract illnesses. In 1967, strains 229E and B814 were found to be indistinguishable from the viral particles of avian infectious bronchitis virus (IBV) when examined by electron microscopy.[440] HCoV-229E is endemic in human populations and causes upper respiratory infections that are more severe in neonates, the elderly, and those with underlying conditions such as a compromised immune system or chronic pulmonary disease.[146] Serum-neutralizing antibody titers are not correlated with protection from reinfection or severity of infection.[184] HCoV-229E uses aminopeptidase N (APN) as a cellular receptor for viral entry, and isolates from around the world having minimal genetic variation.[85] HCoV-229E is closely related to the species *Alpaca alphacoronavirus* and *Dromedary camel alphacoronavirus*. A recent study suggested an evolutionary origin of 229E-related CoVs in hipposiderid bats, hypothetically with camelids as intermediate hosts preceding the establishment of HCoV-229E.[98] HCoV-229E is thought to have emerged in human populations 200 y ago.[155]

Human Coronavirus: HCoV-OC43. *Human coronavirus OC43* (*Betacoronavirus 1*) belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*). In 1967, 6 viral strains that were similar to

Genus/Virus	Primary Host	Target Organ	Host cell	Disease/Symptoms	Transmission	Cell Receptor
Alphacoronavirus						
HCoV-229E	Human	Respiratory tract	Respiratory epithelium	Mild respiratory to pneumonia	Direct contact, aerosol	APN
HCoV-NL63	Human	Respiratory tract	Respiratory epithelium	Mild respiratory to pneumonia	Direct contact, aerosol	ACE2
CCoV	Canine	GI tract	Intestinal epithelium	Enteritis, neurologic signs	Fecal-oral	APN
FCoV	Feline	GI tract	Enterocyte	none to mild gastroenteritis and diarrhea	Direct contact, fecal-oral	FCoV-1: unknown FCoV-2: APN
FIPV	Feline	Systemic	Monocyte Macrophage	Vasculitis, pleural and peritoneal effusion	No direct transmission reported	FCoV-1: unknown FCoV-2: APN
TGEV	Swine	GI tract	Nasal and intestinal epithelium	Diarrhea and vomiting	Fecal-oral, nasal secretions	APN Sialic acids
PEDV	Swine	GI tract	Nasal and intestinal epithelium	Diarrhea and vomiting	Fecal-oral, nasal secretions, aerosol	Sialic acids
PRCoV	Swine	Respiratory tract	Nonciliated respiratory epithelium	Mild respiratory signs	Respiratory droplets and aerosol	APN
SADS-CoV	Swine	GI tract	Intestinal epithelium	Gastroenteritis	Fecal-oral	Unknown
Ferret CoV	Ferret	GI tract or systemic	Enterocyte Macrophage	Gastroenteritis or Systemic pyogranulomatous disease	Fecal-oral (presumed)	Unknown
MCoV	Mink	GI tract	Intestinal epithelium	Gastroenteritis	Fecal-oral	Unknown
Alpaca Resp. CoV	Alpaca	Respiratory tract	Respiratory epithelium	Pneumonia, abortions	Aerosol (presumed)	Unknown
Betacoronavirus						
HCoV-OC43	Human	Respiratory tract, brain	Respiratory epithelium, Neuron	Mild respiratory to pneumonia, encephalitis	Direct contact, aerosol	Sialic acids
HCoV-HKU1	Human	Respiratory tract	Respiratory epithelium	Mild respiratory to pneumonia	Direct contact, aerosol	Sialic acids
SARS-CoV	Human	Respiratory tract	Respiratory epithelium	Mild respiratory to pneumonia	Direct contact, aerosol	ACE2
MERS-CoV	Human (Dromedary Camel - asymptomatic reservoir)	Respiratory and GI tracts, kidney	Respiratory epithelium	Pneumonia, renal failure, diarrhea	Direct contact, aerosol	DPP4
SARS-CoV-2	Human	Respiratory tract	Respiratory epithelium	Mild respiratory to pneumonia, diarrhea	Direct contact, aerosol	ACE2
CRCoV	Canine	Respiratory tract	Respiratory epithelium	Upper respiratory symptoms	Nasal secretions, aerosol	Unknown
PHEV	Swine	GI tract and CNS	Respiratory and small intestine epithelium, Neuron	Vomiting, wasting, and neurologic signs	Direct contact, aerosol	Sialic acids
BCoV	Bovids	Respiratory and GI tracts	Respiratory and intestinal epithelium	Diarrhea, pneumonia	Fecal-oral, aerosol	Sialic acids HLA-1
ECoV	Equine	GI tract	Intestinal epithelium	Gastroenteritis	Fecal-oral, nasal secretions	Unknown
Alpaca Enteric CoV	Alpaca	GI tract	Intestinal epithelium	Gastroenteritis and mesenteric lymphadenopathy	Fecal-oral (presumed)	Sialic acid Heparan sulfate
MHV	Mouse	Respiratory and GI tracts, CNS	Enterocyte, upper respiratory epithelium	Enteritis, hepatitis, encephalomyelitis	Fecal-oral, direct contact, aerosol	CEACAM1
RCoV-P/SDAV	Rat	Respiratory tract, lacrimal, salivary and Harderian glands	respiratory epithelium, acinar epithelium from lacrimal and salivary glands	Pneumonia, keratitis, conjunctivitis, sialodacryoadenitis	Direct contact, aerosol, fomites	Unknown

Figure 3. Summary of Clinical and Pathologic Features of Select Coronaviral Infections.

avian IBV were isolated from adults with upper respiratory illness by using tracheal organ culture.[305] Two strains of this virus, designated OC 38 and OC 43, were subsequently adapted for growth in suckling mouse brain, and reagents prepared from these strains were serologically identical by complement fixation and neutralization tests.[304] Like HCoV-229E, HCoV-OC43 is endemic globally and is the most common human coronavirus; it causes upper respiratory infections in humans. In contrast to HCoV-229E, HCoV-OC43 uses sialic acids on the cell surface as a cellular receptor for viral entry[423] and isolates have significant genetic variability.[452] HCoV-OC43 is naturally capable of invading the central nervous system (CNS), with neurons preferentially targeted for infection.[15] HCoV-OC43 E protein is critical for infectious virus production and for dissemination in epithelial and neuronal cell cultures and mouse CNS and is an important determinant of neurovirulence.[412] Fatal human coronavirus HCoV-OC43 encephalitis has been reported in humans with immune deficiency and, in retrospective studies, associated with multiple sclerosis.[15,223,412] HCoV-OC43 carries an additional structural protein, hemagglutinin-esterase (HE), that binds to sialic acids.[423] HCoV-OC43 is thought to have evolved from ancestral Bovine coronavirus (BCoV) strains that crossed the interspecies barrier and established human infections in around 1890.[107,155] However, BCoV appears to have a rodent origin, *China Rattus coronavirus HKU24*, which crossed species and became established in bovines centuries before the emergence of HCoV-OC43.[262] Enteric coronaviruses antigenically related to HCoV-OC43 have been associated with acute necrotizing gastroenteritis in humans.[166]

Human Coronavirus: HCoV-NL63. *Human coronavirus NL63* belongs to the genus *Alphacoronavirus* (subgenus *Setracovirus*) and was first isolated in 2003 from a 7-mo-old child in the Netherlands who had bronchiolitis and conjunctivitis. The virus was later found to be widespread globally.[446,447] HCoV-NL63 infections usually cause nonfatal upper and lower respiratory tract infections in infants, the elderly, and immunocompromised adults, and have been associated with obstructive laryngitis ('croup') in children.[448] In addition to human primary tracheobronchial cells, HCoV-NL63 replicates and causes a cytopathic effect in tertiary monkey kidney cells and the monkey kidney LLC-MK2 cell line.[160,447] HCoV-NL63 is genetically closely related to HCoV-229E, and its viral genome has distinctive features, including a unique N-terminal fragment in the spike protein.[446] HCoV-NL63 uses human angiotensin-converting enzyme 2 (ACE2) as its cellular receptor.[446] Thought to be of bat origin due to similarity to *NL63-related bat coronavirus strain BtKYNL63-9b*, HcoV-NL63 appears to have emerged in the human population approximately 560 to 820 y ago.[155]

Human Coronavirus: HCoV-HKU1. *Human coronavirus HKU1* (for Hong Kong University) belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*) and was first isolated from a 71-y-old Chinese man admitted to a hospital in Hong Kong in January 2004 because of fever and productive cough with purulent sputum.[483] HCoV-HKU1 is found worldwide and usually causes

Gammacoronavirus						
IBV	Chicken	Respiratory, GI, and reproductive tracts	Respiratory, GI, kidney, and reproductive epithelial cells, cecal lymphoid tissue	Upper respiratory symptoms to pneumonia, renal failure, reduced egg production	Direct contact, fecal-oral, aerosol	Sialic acids
TCoV	Turkey	GI tract	Intestinal epithelium	Diarrhea, skin cyanosis, immune dysfunction	Direct contact, fecal-oral, aerosol	Unknown
PhCoV	Pheasant	Respiratory tract and kidney	Respiratory, renal and reproductive epithelial cells	Upper respiratory symptoms, nephritis, reduced egg production	Direct contact, fecal-oral, aerosol	Unknown
GfCoV	Guinea fowl	GI tract	Intestinal epithelial cells	Diarrhea, pancreatitis	Direct contact, fecal-oral	Sialic acids
BdCoV (HKU22)	Bottlenose dolphin	Respiratory tract	unknown	unknown	unknown	Unknown
BwCoV	Beluga whale	GI tract	unknown	unknown	unknown	Unknown
Deltacoronavirus						
PDCV	Swine	GI tract	Intestinal epithelial cells	Gastroenteritis	Fecal-oral	APN
Uncharacterized						
GpCoV	Guinea Pig	GI tract	Intestinal epithelial cells	Diarrhea, anorexia, and wasting	Fecal-oral (presumed)	Unknown
RECoV	Rabbit	GI tract	Intestinal epithelial cells	Diarrhea	Fecal-oral (presumed)	Unknown
PED/ICV	Rabbit	Cardiovascular system	Cardiomyocyte	Pleural effusion, lung edema, cardiomyopathy, hepatic necrosis, lymphoid depletion	Parenteral inoculation with contaminated stocks of *T. pallidum*	Unknown
Nonhuman primate CoV	Chimpanzee, baboon, macaque, and marmoset	GI tract	Intestinal epithelium	diarrhea	Fecal-oral	Unknown

Abbreviations used:
ACE2 = Angiotensin-Converting Enzyme 2; Alpaca Enteric CoV = Alpaca Enteric Coronavirus; Alpaca Resp. CoV = Alpaca Respiratory Coronavirus; APN = Aminopeptidase N; BCoV = Bovine Coronavirus; BdCoV (HKU22) = Bottlenose Dolphin Coronavirus; BwCoV = Beluga Whale Coronavirus; CCoV = Canine Enteric Coronavirus; CEACAM1 = murine Carcinoembryonic Antigen-related Cell Adhesion Molecule 1; CNS = Central Nervous System; CRCoV = Canine Respiratory Coronavirus; DPP4 = Dipeptidyl-Peptidase 4; ECoV = Equine Coronavirus; FCoV = Feline Coronavirus; Ferret CoV = Ferret Coronavirus; FIPV = Feline Infectious Peritonitis Virus; GfCoV = Guinea Fowl Coronavirus; GI = Gastrointestinal; GpCoV = Guinea Pig Coronavirus; HCoV-229E = Human Coronavirus 229E; HCoV-HKU1 = Human Coronavirus HKU1; HCoV-NL63 = Human Coronavirus NL63; HCoV-OC43 = Human Coronavirus OC43; HLA-1 = Human Leukocyte Antigen class I; IBV = Infectious Bronchitis Virus; MCoV = Mink Coronavirus; MERS-CoV = Middle East Respiratory Syndrome-Coronavirus; MHV = Mouse Hepatitis Virus; PDCV = Porcine Deltacoronavirus; PED/ICV = Rabbit Pleural Effusion Disease/Infectious Cardiomyopathy Virus; PEDV = Porcine Epidemic Diarrhea Virus; PhCoV = Pheasant Coronavirus; PHEV = Porcine Hemagglutinating Encephalomyelitis Virus; PRCoV = Porcine Respiratory Coronavirus; RCoV-P/SDAV = Parker's Rat Coronavirus/Sialodacryoadenitis Virus; RECoV = Rabbit Enteric Coronavirus; SADS-CoV = Swine Acute Diarrhea Syndrome-Coronavirus; SARS-CoV = Severe Acute Respiratory Syndrome-Coronavirus; SARS-CoV-2 = Severe Acute Respiratory Syndrome-Coronavirus-2; TCoV = Turkey Coronavirus; TGEV = Transmissible Gastroenteritis Virus.

Figure 3. (Continued)

mild respiratory disease with rhinorrhea, fever, and cough, but it can also cause more severe disease with febrile seizures, wheezing, pneumonia, and bronchiolitis in very young children, the elderly, adults with chronic respiratory disease, and the immunocompromised; it has also been associated with acute asthmatic exacerbation.[258] Like HCoV-OC43, HCoV-HKU1 carries an additional structural protein, hemagglutinin-esterase, and uses cell surface sialic acids as its cellular receptor for viral entry.[484] HCoV-HKU1 is thought to have emerged in the human population in the early 1950s; a rodent coronavirus is a possible ancestor based on its close relationship to the *Betacoronavirus 1* group and other rodent-associated coronaviruses in the subgenus *Embecovirus*.[107,155,458]

Human Coronavirus: SARS-CoV. *Severe acute respiratory syndrome-related coronavirus* (SARS-CoV) belongs to the genus *Betacoronavirus* (subgenus *Sarbecovirus*). First reported in late 2002 as "atypical pneumonia" in people linked to live animal markets in Guangdong Province of China, SARS-CoV rapidly spread in human populations in China and more than 2 dozen countries in Asia, Europe, North America, and South America, causing the first, well-documented pandemic in modern history.[242,348] By the time SARS-CoV was declared contained in July 2003, over 8,000 cases and 780 deaths had been reported worldwide.[75] Clinical signs included myalgia, headache, fever, malaise, and chills, followed by dyspnea, cough, and respiratory distress; approximately 20% to 30% of the patients required intensive care and mechanical ventilation.[507] In contrast to seasonal coronaviruses, SARS-CoV can affect multiple organs, resulting in high mortality associated with exacerbated host cytokine response.[263]

Autopsy of patients who died due to SARS showed edematous lungs with greyish-brown irregular patches of consolidation, foci of pale tissue of up to several millimeters in diameter, and mucopurulent material in the tracheobronchial tree.[336] Microscopically, bronchial epithelial denudation, loss of cilia, squamous metaplasia, and diffuse alveolar damage were common. Alveolar pneumocytes showed cytomegaly with granular amphophilic cytoplasm along with a giant-cell infiltrate and a pronounced increase in macrophages in the alveoli and interstitium.[336] Coronaviral particles were seen on electron microscopy in the cytoplasm of epithelial cells, and SARS-CoV antigen was found in airways and alveolar epithelial cells, vascular endothelial cells, macrophages, monocytes, and lymphocytes.[177,336] SARS-CoV-infected macrophages expressed CXCL10/IFN-γ-inducible protein 10 and CCL2/monocyte chemotactic protein 1, with poor induction of IFN-β.[84] SARS-CoV-infected dendritic cells showed low expression of antiviral cytokines (IFN-α, IFN-β, IFN-γ, and interleukin 12p40), moderate upregulation of proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, and significant upregulation of inflammatory chemokines (macrophage inflammatory protein 1α, regulated on activation normal T cell expressed and secreted [RANTES], interferon-inducible protein of 10 kDa, and monocyte chemoattractant protein 1 [MCP-1]).[266] In addition, pneumocytes and lung macrophages expressed P-selectin and DC-SIGN.[496] Serum from SARS patients had marked elevation of Th1 IFN-γ, inflammatory cytokines IL-1, IL-6, and IL-12, but no significant elevation of inflammatory cytokine TNF-α, antiinflammatory cytokine IL-10, Th1 cytokine IL-2, and Th2 cytokine IL-4. The serum chemokine profile showed significant elevation of neutrophil chemokine IL-8, MCP-1, and Th1 chemokine IFN-γ-inducible protein-10.[86,482]

Masked palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) in live animal markets in Guangdong

Province of China were identified as carriers of SARS-CoV-like viruses that are almost identical to SARS-CoV.[178] However, wild masked palm civets and farms that were not exposed to live animal markets were negative for SARS-CoV-like viruses, suggesting that these species were intermediate hosts.[398] Although limited research has been conducted to survey wild or farmed raccoon dog populations, they are also considered an intermediate host. The comparative analysis between human and civet SARS-CoVs isolates suggests that SARS-CoV rapidly adapts to different hosts, particularly with mutations at the RBD of the S protein.[407] Like HCoV-NL63, SARS-CoV uses ACE2 as the cellular receptor for viral entry.[277] The search for the natural host of SARS-CoV resulted in the discovery of several SARS-like-CoVs in Chinese horseshoe bats, *Rhinolophus spp*.[198] However, none are considered the immediate parental virus of SARS-CoV.[198] The current model of the origin of SARS-CoV that caused the 2003 pandemic suggests that it is the result of multiple recombination events from several SARS-CoV ancestors in horseshoe bat species in China.[289]

Human Coronavirus: MERS-CoV. *Middle East respiratory syndrome-related coronavirus* (MERS-CoV) belongs to the genus *Betacoronavirus* (subgenus: *Merbecovirus*) and was first reported in June 2012 in Saudi Arabia in a 60-y-old patient with acute pneumonia and renal failure.[501] Clinical signs are similar to those of SARS, characterized by severe respiratory distress; however, a significant number of patients also show renal failure, diarrhea, and vomiting.[5,14,380] MERS cases were mostly independent clusters in Middle Eastern countries, with limited spread to European countries, South Korea, and the United States of America by infected individuals traveling from the Middle East.[145] Since April 2012 and as of May 3rd,2021, 2,589 cases of MERS-CoV, including 940 deaths, have been reported by health authorities worldwide.[141]

Gross lesions reported in a fatal case of MERS-CoV included massive pleural effusion, substantial pericardial effusion, abdominal effusion, edematous and consolidated lungs, and generalized congestion.[334] Microscopic lesions included exudative-phase diffuse alveolar damage with denuding of bronchiolar epithelium, prominent hyaline membranes, alveolar fibrin deposits, type 2 pneumocyte hyperplasia, rare multinucleated syncytial cells, alveolar septal edema with lymphocytes, fewer plasma cells, neutrophils, and macrophages.[334] MERS-CoV antigens were found predominantly in the cytoplasm of pneumocytes and syncytial cells.[334] MERS-CoV infection of human airway epithelial cells induces higher expression of IL-1β, IL-6, and IL-8 than those induced by SARS-CoV.[259] High viral loads, weak antibody responses, and lymphopenia accompanied by thrombocytopenia were associated with disease mortality; persistent lymphocyte responses may be required for effective immunity against MERS-CoV infection.[316] Leukocytosis, primarily due to an increase in neutrophils and monocytes, was generally observed in severe and fatal cases, and blood levels of IL-6, IL-10, IL-15, CXCL-10, TGF-β, and EGF were correlated with disease severity.[233,316]

With a fatality rate of around 35%, MERS-CoV is the deadliest of all coronaviruses known to infect humans.[490] Phylogenetic analysis places MERS-CoV in the same subgenus as bat CoV-HKU4 and bat CoV-HKU5.[486] Bat CoV-HKU4 and MERS-CoV use the same host cell receptor, dipeptidyl peptidase 4 (DPP4), for viral entry.[261,375] However, a bat CoV has not been found that is genetically close enough to be the immediate parental virus of MERS-CoV. Live MERS-CoV identical to the virus found in humans was isolated from the nasal swabs of dromedary camels (*Camelus dromedarius*).[231] Infected camels shed MERS-CoV not only through the respiratory route but also through feces, which is the main route for virus shedding in bats.[187] Another survey found viral RNA and neutralizing antibodies in dromedary camel milk, raising concerns about food-borne transmission of MERS.[372] A recent study in Saudi Arabia found high prevalence (39%) and seropositivity (71%) of MERS-CoV in slaughtered dromedary camels, indicating previous and ongoing MERS infection in this species.[9] The close relationship of MERS-CoV to bat coronaviruses in the *Merbecovirus* subgenus suggests a possible ancestor that crossed host species, adapting to and establishing in camels, which in turn, due to the close contact with humans in the Middle East, sporadically crossed the species barrier and caused outbreaks in humans.[107,188]

Human Coronavirus: SARS-CoV-2 (COVID-19). Coronavirus disease 19 (COVID-19) is recognized by the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses as forming a sister clade to the prototype human and bat SARS-CoVs of the species *Severe acute respiratory syndrome-related coronavirus* and designates it as SARS-CoV-2 (*Severe acute respiratory syndrome-related coronavirus-2*) belonging to the genus *Betacoronavirus*, subgenus *Sarbecovirus*.[171] First reported in the city of Wuhan, China in December 2019, COVID-19 has since spread worldwide. As of March 2nd, 2022, COVID-19 has resulted in more than 438 million confirmed cases and more than 5.9 million deaths.[217] Clinical signs may include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, malaise, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.[76] The majority of the cases are thought to be asymptomatic or mild, with up to 9% of cases, mostly in older people, requiring hospitalization.[308]

The strongest risk factor for severe COVID-19 is age, followed by sex (male), diabetes, hypertension, obesity, chronic kidney disease, and potentially other chronic inflammatory diseases.[426,477] Lung changes at postmortem examination were similar to those seen in SARS and MERS cases characterized by exudative and proliferative phases of diffuse alveolar damage, with capillary congestion, necrosis of pneumocytes, hyaline membranes, interstitial and intraalveolar edema, type 2 pneumocyte hyperplasia, squamous metaplasia with atypia, and platelet-fibrin thrombi.[64] The inflammatory infiltrate was largely composed of macrophages in the alveolar lumen and lymphocytes in the interstitium.[64] Electron microscopy revealed that viral particles were predominantly located in pneumocytes.[64] SARS-CoV-2 evades innate immunity response through the expression of viral nonstructural proteins that block IFN pathways, resulting in lower levels of IFN-I and IFN-III in the lungs and peripheral blood.[224] Genetic mutations or autoantibodies that interfere with IFN pathways may also increase the susceptibility to severe COVID-19 disease. On the other hand, prolonged secretion of IFN during the late phase of the infection correlates with disease severity, most likely due to the induction of chemokines that recruit inflammatory cells.[268,288] Patients with severe COVID-19 have a marked decline in the number of dendritic cells, T cells, and NK cells in the blood, along with depleted alveolar macrophages and dendritic cells in the lungs, all of which result in a severe reduction of the host's ability to mount an effective immune response.[288,300,473,511] CD4+ and CD8+ T cells directed against multiple SARS-CoV-2 antigens, including structural and nonstructural proteins, are significantly associated with milder disease, suggesting that a coordinated CD4+ T cell, CD8+ T cell, and antibody response is required for protection against severe disease.[379] In severe cases, tissue damage persists after viral clearance due to an exacerbated immune response that can cause pulmonary endothelial injury, excess vascular

permeability and microthrombi deposition.[357] Extrapulmonary pathology is predominantly seen in the liver and spleen, with intravascular thrombosis commonly being widespread and with disseminated intravascular coagulation often present.[313] Other common findings are gastrointestinal symptoms and cardiac, renal, and olfactory dysfunction.[286,357,494] The pathogenesis of the extrapulmonary lesions is most likely multifactorial due to direct viral injury to cells and to an exacerbated/dysfunctional immune response damaging multiple tissues.

Similar to HCoV-NL63 and SARS-CoV, SARS-CoV-2 uses host ACE2 as the cellular receptor for viral entry.[425] Many of the initial cases of COVID-19 were associated with the Huanan Seafood Wholesale Market, which sells wildlife species, suggesting a probable zoonotic origin.[274] Pangolins (*Manis javanica*) were recently found to carry beta-CoVs that have 85% to 92% nucleotide sequence homology with SARS-CoV-2.[295] In addition, the intermediate horseshoe bat (*Rhinolophus affinis*) carries a coronavirus (CoV RaTG13) that has 96% nucleotide homology with SARS-CoV-2.[295] However, despite these close relationships, the sequence divergence is too great for these animal CoVs to be the immediate parental strain for SARS-CoV-2.[295] The animal reservoir and origin of SARS-CoV-2 remain to be determined.

Coronaviruses of Domestic Animals

Domestic fowl coronaviruses. While the SARS-CoV-2 pandemic has placed the spotlight on human CoVs, the first CoV ever described was Infectious Bronchitis Virus (IBV) in domestic chickens over 80 y ago.[72] All bird CoVs described to date are either gamma- or deltacoronaviruses, whereas most mammalian CoVs are alpha- or betacoronaviruses.[130] Domestic fowl CoVs belong to the genus *Gammacoronavirus* (subgenus *Igacovirus*), species *Avian coronavirus*. The study of IBV and other bird CoVs has provided a wealth of information on coronaviral structure and function, disease pathogenesis, and vaccine strategies. However, despite decades of research on IBV, the disease still causes significant economic losses around the world.[130] CoVs of domestic and wild bird populations have been found on all continents,[474] and migratory, wild birds are the suspected reservoir for recurring outbreaks in domestic fowl.

Infectious bronchitis virus (IBV). Infectious bronchitis of newborn domestic chickens (*Gallus gallus domesticus*) was first reported in 1931, and a viral etiology was described in 1936.[474] Clinical signs in young chicks included ocular/nasal discharge, coughing, sneezing, swollen sinuses and respiratory rales, and reduced feed consumption and weight gain, with mortality reaching 90%.[211] Although the clinical signs in young chicks are primarily respiratory, the virus can replicate in numerous epithelial surfaces, including the GI tract, kidney, and reproductive tract.[71] IBV uses the host cell sialic acids for attachment.[478] The respiratory lesions caused by IBV often lead to secondary viral and bacterial infections that exacerbate disease severity.[92] Some strains cause severe renal disease and high mortality in adults; whereas others cause reduced egg production and egg quality.[211] Persistent infections of the cecal lymphoid tissue and kidneys are likely to be a source of recurrent outbreaks in flocks.[92] Morbidity in flocks quickly reaches 100%, resulting in high viral replication and the emergence of mutant strains. To date, at least 32 different IBV serotypes or strains have been reported around the world.[474] Transmission is by direct contact with infected birds or contaminated fomites such as bedding and equipment.[211] Vertical transmission does not appear to occur.[92] Sialic acids are the dominant cellular receptors to which IBV binds and enters cells.

Turkey coronavirus (TCoV). Coronaviral infection in domestic turkeys (*Meleagris gallopavo domesticus*) was first reported in the US in 1951 as severe gastrointestinal disease in young poults with high morbidity and mortality.[360] The disease also caused cyanosis of the head and was termed 'Bluecomb disease.' The etiological agent was identified as a coronavirus in the 1970s.[385] Turkey coronavirus (TCoV) was not found in European turkey poults until 2008.[130] Poults up to 4 wk of age are the most susceptible to severe disease and mortality. The virus targets the intestinal epithelium and cloacal bursa.[385] Clinical signs include anorexia, depression, decreased feed consumption, watery diarrhea, and high mortality.[208] The virus causes atrophy of the thymus and bursa of Fabricus, leading to immune dysfunction and the promotion of secondary infections.[60] Turkey coronavirus is one of several infectious agents involved in poultry enteritis-mortality syndrome (PEMS).[130] TCoV is antigenically similar to IBV, and chickens can develop asymptomatic infections with TCoV.[208] Experimentally, turkeys can be infected with bovine coronavirus (BCoV) and develop mild enteritis; however, natural BCoV infections have not been reported.[71]

Pheasant coronavirus (PhCoV). Farmed, domestic pheasants (*Phasianus colchicus*) were first reported to develop coronaviral disease in the UK in the early 1980s.[408] The disease causes high mortality (45%) in young birds with nonspecific clinical signs such as hunched posture and drooping wings, although some reports found mild respiratory signs.[71,186] Affected adult females had reduced egg production and occasional abnormalities in egg quality.[186] Nephritis has also been reported.[71,186] Similar to TCoV, chickens experimentally inoculated with PhCoV developed neutralizing antibodies but no disease.[71] The cellular receptor used by PhCoV is currently unknown but likely is sialic acids similar to IBV.[186]

Guinea fowl coronavirus (GfCoV). Acute enteritis in farmed guinea fowl (*Numida meleagris*), known as Fulminating Disease (or X-disease), was first described in France in the 1980s; however, an etiology was not identified until 2011.[280] While initial reports appeared to point to an avian *Gammacoronavirus* as the sole etiological agent,[133,280] no studies have reported successful, experimental infection with purified guinea fowl coronavirus (GfCoV). To date, Fulminating Disease of guinea fowl is associated with infections of both GfCoV and either a guinea fowl astrovirus (GfAstV)[434] or a guinea fowl picornavirus (GfPic).[101] In vitro experiments have shown that GfCoV binds to sialic acid receptors.[57] The disease has a very high mortality rate; lesions are most often limited to the GI tract but may occasionally be found in the pancreas.[57]

Canine coronaviruses. Canine coronaviruses are usually associated with mild, self-limiting disease. The 2 forms of canine coronavirus are canine enteric coronavirus (CCoV), which belongs to the genus *Alphacoronavirus* (subgenus *Tegacovirus*) species *Alphacoronavirus 1*, and the canine respiratory coronavirus (CRCoV), which belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*) species *Betacoronavirus 1*.[115,116,139,321]

Canine enteric coronavirus (CCoV). CCoV is associated with enteric disease and was first isolated in 1971 from military dogs with mild enteritis.[53] Currently, CCoV has worldwide distribution, is commonly associated with gastrointestinal disease of varied severity, and is caused by 2 subtypes.[115,410,460] It also has been found in wild canids.[8,324] CCoV is related to feline coronavirus (FCoV) and swine transmissible gastroenteritis virus (TGEV).[65,282] More recently, a CCoV strain recombinant with TGEV has been isolated (CCoV-2b).[122] Two serotypes (CCoV-1 and CCoV-2) and mixed serotype infections are common in outbreaks.[115,460] Based on genetic sequencing, the 2 serotypes

differ in their S proteins, [116,282,361] which have different amino acid sequences in the N-terminal region.[121] In addition, the detection of the recombinant strains resulted in the serotype 2 reclassification as CCoV-2a and CCoV-2b for the recombinant strains.[121,122] CCoVs are transmitted via the fecal-oral route using APN as the cellular receptor.[42] Outbreaks are associated with young dogs in kennels or shelters.[410] Based on the virulence of CCoV, 2 different pathogenic phenotypes have emerged but do not coincide with the serotype.[428] CCoV-1 and CCoV-2 can cause asymptomatic or self-limiting (mild) enteritis or systemic disease with fever, enteritis, and/or neurologic signs.[61] A highly virulent CCoV-2a strain has emerged, resulting in pantropic (systemic) infection not restricted to the gastrointestinal system.[119] More severe disease has also often been associated with mixed infection with other pathogens and are age dependent, with puppies being more susceptible to clinical disease.[91,116] Infected dogs usually present with an acute onset of diarrhea, vomiting, loss of appetite and lethargy. Clinical signs of less virulent strains resolve in 8 to 10 d. CCoV-1 isolates do not propagate easily in cell culture; CCoV-2 does propagate in cell cultures such as canine tumor fibroblast.[282]

Canine respiratory coronavirus (CRCoV). First described in 2003, CRCoV is associated with respiratory disease with mild to severe clinical signs.[139,363] It is considered an infectious agents in canine infectious respiratory disease (CIRD) and is commonly associated with respiratory disease outbreaks in kennels.[139,321,363] CRCoV is closely related to bovine coronavirus.[139] CRCoV is most likely transmitted via respiratory secretions, with dogs older than 1 y having greater seroprevalence.[139] It has a high tropism for canine upper respiratory tissues, causing an acute mild respiratory infection with clinical signs such as a dry cough or nasal discharge.[139,321,363] Clinical disease can worsen with coinfections of other respiratory pathogens.[363] The cellular receptor used by CRCoV to infect host cells is currently unknown.

Feline coronavirus (FCoV). Feline Coronavirus (FCoV), first described in 1977, can cause disease in both domestic and wild cats.[229,417] Like CCoV, FCoV belong to the *Alphacoronavirus* genus (subgenus *Tegacovirus*) species *Alphacoronavirus 1.* FCoV has 2 serotypes (type 1 and type 2).[213] FCoV-1 is considered the ancestor lineage and is the predominant virus circulating in domestic cat populations, which are approximately 20% to 60% seropositive.[3,214,429] FCoV-2 emerged from a recombination between FCoV-1 and CCoV-2 and is less common.[213,429] However, FCoV-2 is easier to propagate in cell culture, such that most studies use the less common virus.[213] FCoVs are related to both canine enteric coronavirus and transmissible gastroenteritis virus of pigs.[192] FCoVs have been studied intensely because the 2 biotypes can cause either asymptomatic or mild enteric clinical signs (Feline Enteric Coronavirus, or FECV), or a virulent, fatal systemic disease (Feline Infectious Peritonitis Virus, or FIPV).[213,265,417] Both biotypes can occur with either serotype.[213,429]

FCoV is a highly contagious pathogen with a fecal-oral route of transmission.[73,147,235] In animal shelters, multicat households, or catteries, an estimate of 90% seropositive rate may occur.[74,429] The biotype FECV is often subclinical or causes mild transient gastrointestinal signs in cats.[346,429] During primary infection, FECV is shed at higher levels in kittens than in adult cats.[346] Cats may remain persistently infected, which results in a high seropositive rate in settings that house multiple cats. In contrast, the virulent biotype FIPV causes an immune mediated lethal disease known as Feline Infectious Peritonitis (FIP). The disease is most common in young cats (less than 3-y-old).[209,230] Although the initial infection is like FECV, with the viral tropism affecting the intestinal epithelial cells, the virus mutates and gains the ability to enter and replicate in monocytes and macrophages.[214,230] The mutation occurs on the S protein glycoprotein and allows more efficient replication in macrophages and monocytes,[230,283] resulting in systemic distribution and severe disease in the affected cat. However, FIPV either is not shed or is shed at low levels, and therefore does not cause FIP epidemics.[213,230,429] The severity of disease varies on host factors such as major histocompatibility complex (MHC) characteristics, cytokine responses, and the cell-mediated immune (CMI) response.[2,230] Cats that with FIP mount a more robust humoral as opposed to CMI response; these varying responses result in the different clinical signs.[230] FIP is characterized by its clinical presentation as effusive (wet), noneffusive (dry), or a combination of the 2.[429] The effusive form has a rapid course due to vasculitis causing protein-rich fluid in body cavities. Cats with the noneffusive form have a stronger T-cell response than do cats with the effusive form.[429] Genetic predisposition and immunosuppression caused by stress or other disease increase the risk of overt disease.[230,429] FCoV uses APN as a cellular receptor.[437]

Swine Enteric Coronavirus Disease (SECD). SECD refers to all swine coronaviruses that cause gastrointestinal disease, including swine transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV), porcine deltacoronavirus (PDCoV), swine acute diarrhea syndrome-coronavirus (SADS-CoV), and the recently described chimeric swine enteric coronavirus (SeCoV).

TGEV belongs to the genus *Alphacoronavirus* (subgenus *Tegacovirus)*, species *Alphacoronavirus 1* (along with canine coronavirus, feline coronavirus, and porcine respiratory coronavirus). TGEV was first reported in 1946 in the United States as a highly infectious disease causing acute severe diarrhea and vomiting in pigs. TGEV is the oldest known swine disease caused by a coronavirus.[132] The host cell receptor used by TGEV is APN, a multifunction protein that is expressed in several tissues including intestinal, renal, respiratory, and nervous.[125,317] In addition , a second, unidentified cell receptor has been proposed for the intestinal villi of neonatal pigs.[464] TGEV has an affinity for sialic acids, which facilitates enteric infections.[394] Fatal infections are more common in piglets born to seronegative sows, approaching 100% piglet mortality rate.[162,189] An endemic form of the disease occurs in herds with partial immunity or concurrent viral respiratory infections, with less severe signs and very low mortality.[39,189,364] TGEV in piglets cause small intestinal epithelium atrophy and necrosis with reduced crypt height and depth, resulting in malabsorption syndrome; it also impairs the intestinal mucosal immune response, predisposing piglets to infection by other pathogens and by elevated expression of inflammatory cytokines.[492] Infected sows can transmit virus to piglets in their milk or feces. Although small intestine villous epithelial cells are the main site of viral replication and feces are the major source of infection through the fecal-oral route, the virus also replicates in the upper respiratory epithelial cells and is shed through nasal secretions with potential airborne spread for over a short distance.[58,449] Depending on the age of the pig, infection with TGEV results in viremia with wide viral distribution in the body.[157] Fecal shedding generally lasts for 2 wk after exposure, and respiratory shedding for up to 11 d after exposure, but chronic carriers can shed for up to 104 d after infection.[226,227,351,442] Transmission also occurs through fomites.

PEDV belongs to the genus *Alphacoronavirus* (subgenus *Pedacovirus).* Genetic analysis found that PEDV is closely related to the species *Scotophilus bat coronavirus 512*, suggesting that

cross-species transmission possibly occurred between bats and pigs.[19] PEDV was first described in Europe in 1971, in the 1990s in Asia, and not until 2013 in North America, as a highly infectious enteric disease characterized by acute gastroenteritis with watery diarrhea, vomiting, and dehydration.[77,81,202,352,421,488] Infections are nearly 100% fatal in piglets born to seronegative sows. Transmission is fecal-oral but airborne transmission via the fecal-nasal route has also been described.[10,103] PEDV was originally reported to use APN as a cell receptor,[273] but later studies suggest an additional cellular receptor independent of APN for PEDV entry.[215,399,472] Similar to TGEV, PEDV can also bind sialic acids.[126,275] PEDV can infect multiple cell lines in vitro from species other than pigs, porcine including bats and primates.[284] The virus can infect nasal epithelial cells and the dendritic cells in the nasal submucosa, which in turn delivers the virus to CD3 + T cells that are carried by blood and lymph circulation to the intestinal epithelial cells.[279] PEDV mainly infects small intestine epithelial cells, causing atrophy of the intestinal villi and resulting in malabsorption and dyspepsia.[221] One report suggests PEDV infects pig alveolar macrophages and may cause lesions in the lungs.[343] Two different PEDV genotypes have been described based on the S gene; these are Genogroup 1 and Genogroup 2, which are further divided into subgenotypes.[455] Natural recombination between the PEDV genotypes has been described along with recombination between PEDV and TGEV.[4,55] This novel chimeric swine enteric coronavirus (SeCoV) contains a genome background identical to TGEV but expresses the S gene and 3a protein sequences from PEDV.[41] SeCoV was isolated from all cases of diarrhea, supporting its virulence.[4,41,55] SeCoV appears to continue to circulate in Europe and cause a disease very similar to PEDV.[41] In addition to the novel chimeric SeCoV, the full-length genome sequence analysis of a PEDV field isolate in China (CH/HNQX-3/14) showed unique deletion regions in the S and ORF3 genes.[275] Further analyses suggested that CH/HNQX-3/14 is a natural recombinant of the attenuated vaccine strains (CV777 and DR13) and the circulating wild-type strain (CH/ZMDZY/11).[275] The recombination occurred not only in the structural protein-coding region (S1 and N genes) but also in the nonstructural protein-coding region (replicases 1a and ORF3 genes). These findings suggest that PEDV strains circulating in China underwent recombination between vaccine and field strains, contributing to the genetic diversity of PEDV.[275]

PDCoV belongs to the genus *Deltacoronavirus* (subgenus *Buldecovirus*), species *Coronavirus HKU15.* PDCoV was first described in 2012 in Hong Kong during a large coronavirus molecular survey of mammals and birds.[487] Genetic analysis found PDCoV to be closely related to 2 avian deltacoronaviruses, suggesting a common avian coronavirus as an ancestor.[220] Similar to PEDV and TGEV, PDCoV causes gastroenteritis characterized by watery diarrhea and vomiting in sows and nursing pigs. However, mortality in piglets is lower than that of PEDV and TGEV infections.[406] Microscopic lesions include acute necrosis of intestinal epithelial cells with villus shortening and intestinal wall thinning, resulting in malabsorption.[460] The main infection route appears to be fecal-oral.[220] PDCoV uses APN as a cell receptor and have a second receptor that is not yet identified.[497] PDCoV can experimentally infect calves, poultry, and human cell lines, making it a potential threat to public health and other farm animal species.[497]

SADS-CoV, also called swine enteric alphacoronavirus (SeACoV), belongs to the genus *Alphacoronavirus* (subgenus *Rhinacovirus*), and is considered the same species as bat coronavirus *Rhinolophus bat coronavirus HKU2*; both appear to descend from a common ancestor.[509] SADS-CoV is the most recent swine coronavirus, first reported in China in 2017 as a cause of severe diarrhea with high mortality in neonatal piglets.[342] Transmission is through the fecal-oral route.[342,509] The cell receptor is currently unknown but in vitro studies suggest that SADS-CoV does not require any of the known coronavirus cell receptors to infect a variety of mammalian cell lines.[136] Clinical signs are similar to other porcine enteric coronaviruses, which produce acute gastroenteritis characterized by vomiting, diarrhea, and high mortality in newborn piglets.[342,509] The virus affects the small intestine, mainly the jejunum and ileum, causing necrosis of the epithelial cells resulting in atrophy and shortening of the villi.[509]

Porcine hemagglutinating encephalomyelitis virus (PHEV). PHEV belongs to the genus *Betacoronavirus* (subgenus *Embecovirus)* species *Betacoronavirus 1* along with bovine coronavirus, human coronavirus OC43, equine coronavirus, alpaca coronavirus, dromedary camel coronavirus UAE-HKU23, and canine respiratory coronavirus, and they likely share a common ancestor.[206] PHEV was first described in Canada in1957 as causing vomiting, wasting disease, and encephalomyelitis in piglets; the virus was isolated a few years later.[176,374] The disease is relatively infrequent because piglets are usually protected by maternal colostral antibodies until they develop resistance to the disease.[293,325] Clinically, the piglets typically vomit after feeding and show anorexia, depression, and progressive emaciation. Piglets with neurologic signs may show dog-sitting posture, muscle tremors, opisthotonos, convulsions, paddling movements, or paralysis.[67,175,176] The virus is shed in nasal secretions, and infection occurs through aerosols and contact with secretions from infected pigs.[326] The virus first multiplies in the nasal epithelium, tonsils, lungs, and small intestine before spreading to the CNS via peripheral nerves.[12,13] PHEV uses 9-*O*-acetylated sialic acid as a host cell receptor.[301] The clinical signs appear to be related to viral infection of vagal sensory ganglia, inducing vomiting, and gastric myenteric plexuses, causing delayed emptying of the stomach.[12] At necropsy, PHEV-affected pigs show cachexia, stomach distention containing nondigested milk, and, in chronically infected piglets, abdominal distension.[293] Microscopic changes in piglets with neurologic signs may include lymphoplasmacytic perivascular cuffing and mononuclear cell infiltration, gliosis, neuronal death, and satellitosis affecting the gray matter of the cerebrum.[468] In piglets with vomiting and wasting, degeneration of the ganglia of the stomach wall and lymphoplasmacytic perivascular cuffing are the most common findings.[108,389]

Porcine respiratory coronavirus (PRCoV). PRCoV belongs to the genus *Alphacoronavirus* (subgenus *Tegacovirus*), species *Alphacoronavirus 1*, along with canine coronavirus, feline coronavirus, and TGEV. First described in Europe in1986, PRCoV causes a mild or subclinical respiratory disease in swine of all ages.[350] PRCoV is a genetic variant of TGEV with a deletion of variable size in the spike protein that causes the loss of sialic acid binding activity with consequent changes in major tissue tropism from enteric to respiratory epithelium.[392,394] PRCoV shares some epitopes for neutralizing antibodies with TGEV, resulting in PRCoV antibodies providing strong immunity against TGEV infection.[45,112,138,470] Transmission is through respiratory droplets and aerosols. The virus uses APN as a cell receptor and preferentially targets nonciliated, nonmucus producing cells in the respiratory epithelium, replicating in tonsils, respiratory mucosal epithelium, and in both type I and II pneumocytes and causing inflammation and necrosis.[102] PRCoV also infects, but to a very low degree, cells from the small intestine.[102] The infection is usually asymptomatic but can cause mild fever,

dyspnea, polypnea, anorexia, and, at necropsy, bronchiointerstitial pneumonia.[102]

Bovine coronavirus (BCoV). Bovine coronavirus (BCoV) belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*), a prototype of the species *Betacoronavirus 1* along with HCoV-OC43, equine coronavirus, alpaca coronavirus, dromedary camel coronavirus UAE-HKU23, PHEV, and CRCoV, all caused by *Betacoronavirus 1* species.[206] The virus was first reported in 1972 as a coronavirus-like agent associated with spontaneous neonatal calf diarrhea with high mortality.[409] Shortly thereafter a coronavirus was confirmed to be the cause of diarrhea by experimental infection of neonatal calves, and the virus was then quickly isolated and characterized.[306,307] BCoV attaches to host cell surface sialic acids and appears to use human leukocyte antigen class I (HLA-1) as the entry receptor, resulting in wide viral cellular tropism.[423] BCoV also contains a surface hemagglutinin-esterase (HE) glycoprotein that mediates reversible attachment to *O*-acetylated sialic acids by acting both as lectins and as a receptor-destroying enzyme (esterase) to reverse hemagglutination.[384,503] BCoV causes 3 distinct clinical syndromes in cattle: neonatal calf diarrhea, "winter dysentery" in lactating cows, and "shipping fever", a respiratory disease in feedlot cattle.[384] Morbidity is high, but mortality is generally low, except in calves in which passive immunity from mother's milk begins to wane.[117] Viral shedding occurs through feces and nasal secretions, and transmission is via the fecal-oral route or through the inhalation of aerosols. Shedding usually lasts up to 10 d in calves and up to 45 d in adult cattle, but prolonged intermittent shedding has been reported in asymptomatic animals.[222,338,384] Low titers of ocular viral shedding has also been reported.[117] The virus initially replicates in the nasal mucosa and is believed to spread to the gastrointestinal tract after the animal swallows large quantities of the virus that is protected by mucous secretions, resulting in intestinal infection and fecal shedding.[384] BCoV causes extensive necrosis of the large intestinal mucosa, resulting in malabsorption and severe loss of water and electrolytes that is more severe in very young animals.[307] In adult cattle, the extensive mucosal intestinal necrosis is usually accompanied by hemorrhage.[54,117] BCoV infection of the respiratory tract appears to predispose cattle to secondary bacterial infections aggravated by transport stress resulting in "shipping fever" pneumonia, characterized by an often-fatal fibrinous bronchopneumonia.[143,416] BCoV-like coronaviruses have been found in different species of wild ruminants suggesting a potential role as reservoirs.[7,439] BCoV was recently suggested to originate from a rodent CoV after a novel CoV species, phylogenetically intermediate between BCoV and MHV, was described in Norway rats in China (*China Rattus Coronavirus HKU24*). The finding of this new virus suggests rodents as possible reservoirs for CoVs in the subgenus *Embecovirus* and possible ancestors of BCoV.[99,262]

Equine coronavirus (ECoV). Equine coronavirus (ECoV) belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*), assigned to the species *Betacoronavirus 1* along with HCoV-OC43, BCoV, alpaca coronavirus, dromedary camel coronavirus UAE-HKU23, PHEV, and CRCoV.[206] ECoV was first isolated and characterized in 2000 from a neonatal foal with enterocolitis.[110,180] However, reports of the association between coronaviruses and gastroenteritis in foals goes back to 1975.[38,201] ECoV causes sporadic outbreaks and infections in horses in America, Europe, and Asia.[151,167,170,188,320,332,368] The most common clinical signs include anorexia, fever, lethargy, and leukopenia, followed by diarrhea, colic, and less often, neurologic signs.[46,151,167,302,368,369] ECoV infections are usually self-limiting or subclinical; however, one report in miniature horses found that 27% of the animals died or were euthanized.[151,387] In severe cases, mortality may occur due to loss of intestinal mucosa barrier function, resulting in septicemia, endotoxemia, and hyperammonemia-associated encephalopathy.[167] Pathology findings include diffuse necrotizing enteritis characterized by marked intestinal villus attenuation, necrosis of apical enterocytes with pseudomembrane formation, and hemorrhage with mucosal microthrombi.[167] Horses with neurologic signs may have diffuse Alzheimer type II astrocyte hypertrophy and hyperplasia in the cerebral cortex.[167] Experimental infection of horses with ECoV showed that infected horses intermittently excreted large amounts of virus in their feces for over 9 d after inoculation, regardless of the presence or absence of clinical signs, highlighting the significance of fecal-oral transmission.[331,367,387] ECoV was also detected in nasal swabs from experimentally infected horses, suggesting that respiratory transmission may occur.[331,367,387] Viremia was detected only in symptomatic horses.[331] The cellular entry receptor has yet to be identified. Complete genome sequences of ECoV isolates from the United States and Japan show close sequence homology ranging from 98 to 99%.[332] Phylogenetic analysis showed ECoV is most closely related to BCoV, HCoV-OC43, and PHEV, and may have emerged earlier despite not being isolated until 1999 from a foal with diarrhea.[180,505] The ECoV nsp3 protein has considerable amino acid deletions and insertions compared with the nsp3 proteins of BCoV, HCoV-OC43, and PHEV.[505]

Ferret coronavirus. Ferret coronaviruses belong to the genus *Alphacoronavirus* (subgenus *Minacovirus*). Ferret coronaviruses are closely related to *Mink coronavirus 1* with a new species designation, *Alphacoronavirus 2*, more recently suggested for both ferret and mink coronaviruses.[254] First reported in the United States in 1993 as epizootic catarrhal enteritis in domestic ferrets (*Mustela putorius furo*), the disease was associated with a coronavirus in 2000.[475] Infection with ferret coronavirus can result in enteric or systemic disease. Systemic disease could be caused by a mutation of the coronavirus in the infected ferret; recombination in ferret coronaviruses resulting in novel strains have been recently described.[254,318,428,493] Complete genome sequencing of enteric and systemic ferret coronavirus strains shows 89% nucleotide similarity, with much less similarity to other known alphacoronaviruses (50% to 69% nucleotide identity).[276,431,479,480] The cellular entry receptors used by ferret coronaviruses have not been identified. Clinically, the enteric disease is characterized by profuse, bright green, mucoid diarrhea with a foul smell, along with anorexia, lethargy, and vomiting.[475] Mortality is usually low. Severe disease is more common in older ferrets with concurrent diseases such as insulinoma, adrenal-associated endocrinopathy, and long-standing gastric infection with *Helicobacter mustelae*, while young ferrets often show mild disease and may be subclinical carriers.[475] Lesions are limited to the gastroenteric tract and characterized by fusion and blunting of villi, vacuolar degeneration and necrosis of apical villous enterocytes, and lymphocytic enteritis.[475] A second clinical form of the disease, ferret systemic coronavirus, was first reported in Spain in 2004; genetic analysis found this virus to be closely related to ferret enteric coronavirus.[298] The disease is similar to the dry form of FIP in cats, with ferrets showing a systemic and progressive pyogranulomatous inflammatory disease with high mortality.[161] Affected ferrets are usually young and may show a wide range of clinical signs including chronic weight loss, anemia, anorexia, vomiting, cough, fever, weakness, diarrhea, rectal prolapse, icterus, skin erythema, abdominal masses/organomegaly, heart murmurs, and neurologic signs.[161,359] Blood and

serum chemistry panels commonly show anemia, neutrophilic leukocytosis, thrombocytopenia, hyperproteinemia, hypergammaglobulinemia, hypoalbuminemia, azotemia, elevated alanine aminotransferase, and serum lipase.[161,359]

Mink coronavirus (MCoV). Mink coronavirus (MCoV), or Mink Epizootic Catarrhal Gastroenteritis, belongs to the genus *Alphacoronavirus* (subgenus *Minacovirus*), species *Mink coronavirus 1*. The disease was first described in the United States in 1975 as mucoid diarrhea and anorexia over a 2 to 6-d course, particularly during the fall, with what seems genetic predilection in dark colored mink.[256] Mortality is generally low (<5%) unless a concurrent viral or bacterial infection occurs.[172,256] The etiological agent was identified in 1990 by electron microscopy as a coronavirus.[172] Serologic studies showed that MCoV cross reacts with pig TGEV and PEDV.[172] A more recent genomic analysis placed MCoV isolates in the *Alphacoronavirus* genus, closely related to ferret coronaviruses.[454] MCoV appears to be common in farmed mink in North America, Denmark, the Netherlands, Russia, Belarus, Estonia, Latvia, Lithuania, and China.[172] The presence of coronavirus particles in feces after natural and and experimental infection suggests that transmission may be fecal-oral with viral shedding beginning 2 d after infection and continuing for 2 wk.[172] Some mink are asymptomatic carriers.[172] The cellular receptor has not yet been identified.

Alpaca coronaviruses. *Alpaca enteric coronavirus.* Alpaca enteric coronavirus (ACoV) belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*), a member of the *Betacoronavirus 1* species complex, with sequence analysis showing a close relationships to BCoV (> 99.5% nucleotide identity), HCoV-OC43 (> 96%), and PHEV (> 93%).[216] The disease was first reported in 1998 associated with outbreaks of severe diarrhea in young and adult llamas and alpacas.[290,376,471] Other members of the *Betacoronavirus 1* species complex use sialic acids or heparan sulfate on the cell surface for attachment but this has not been determined for ACoV.[423] Gross lesions reported on a single animal included mixed watery and mucoid intestinal contents, diffuse thickening of the wall of the third gastric compartment, and mesenteric lymphadenopathy. Microscopically, the small intestine showed diffuse edema of the lamina propria and submucosa with multifocal petechia, necrotic debris within intestinal crypts, and fibrinopurulent hemorrhagic mesenteric lymph nodes.[164] BCoV may be the ancestor of ACoV, with cross-species transmission occurring when cattle were introduced in South America 500 y ago, as New World camelids graze at lower altitudes during winter and share pastures with cattle.[74,290,373]

Alpaca respiratory coronavirus. Alpaca respiratory coronavirus belongs to the genus *Alphacoronavirus* (subgenus *Duvinacovirus*). The virus was isolated in 2007 in association with an outbreak of acute respiratory disease and abortions in alpacas after participation in a large animal exposition.[105] Genome sequencing suggests alpaca alphacoronavirus is closely related to HCoV-229E with 92% nucleotide identity.[106] Spike gene sequences from alpaca alphacoronavirus and from HCoV-229E isolates recovered over several decades showed alpaca respiratory coronavirus to be most similar to HCoV-229E viruses isolated in the 1960s to early 1980s, suggesting that cross species transmission might have occurred during that time.[106] No other outbreaks have been reported. Clinical signs vary from mild upper respiratory disease to severe respiratory distress, fever, and death.[105] Abortions appear to be related to severe fetal hypoxia in pregnant alpacas with severe respiratory distress.[105] Necropsy findings include marked pulmonary congestion with edema and pleural effusion.[105] Microscopically, diffuse interstitial to bronchointerstitial pneumonia with congestion and edema were the most prominent findings, along with fibrin deposition and hyaline membrane formation on terminal airways and epithelial necrosis.[105] The cellular receptor used by alpaca alphacoronavirus to infect the host cell is unknown but based on the close genetic relationship to HcoV-229E, and like most alphacoronaviruses, it may use APN for cell attachment.[106]

Coronaviruses in Research Species

Mouse hepatitis virus (MHV). The species *Murine coronavirus,* better known as Mouse Hepatitis Virus (MHV), belongs to the genus *Betacoronavirus* (subgenus *Embecovirus*). Isolated in 1949, the virus was named Murine Virus JHM after J. Harold Mueller.[29] This virus caused disseminated encephalomyelitis accompanied by extensive destruction of myelin in the CNS and focal necrosis of the liver.[82] Two years later, a similar virus was isolated from young mice dying from hepatitis; the new virus was called Mouse Hepatitis Virus.[168] The name mouse hepatitis virus prevailed, and later "lethal intestinal virus of infant mice" (LIVIM), a disease known for years and suspected to be of viral origin, was found to be caused by MHV.[66,207] MHV is a natural pathogen of mice, with multiple strains described that differ in organotropism, virulence, and pathogenicity, and are broadly classified in 2 groups, enterotropic and polytropic.[293] However, due to the inherent property of these viruses to constantly mutate and recombine within mouse populations, isolates show considerable overlap.[293]

Enterotropic MHV (LIVIM) is a, highly contagious infection, causing close to 100% mortality among infant mice when introduced to a naïve population.[240] Common enteric strains of MHV that cause the characteristic intestinal disease in infant mice include MHV-Y, MHV-RI, MHV-D, and MHV-S/CDC.[193,196,197,250,293] Enterotropic strains tend to be highly contagious and restricted largely to the intestine but, depending on the virus strain and host factors, can spread to other organs, mainly the liver, lymphoid tissue, spleen, and sometimes the brain.[25,27,31] In neonates, enterotropic MHV induces rapid cytolysis of terminally differentiated enterocytes that line the intestinal villi. Infant mice have shallow slow-replicating intestinal crypt progenitors, allowing rapid loss of enterocytes after infection with enterotropic MHV. Affected mice show segmental epithelial necrosis, villus attenuation, mucosal erosion, and epithelial syncytia affecting the terminal small intestine, cecum, and proximal colon.[27] As mice get older, the intestinal mucosa responds more quickly to the virus, regenerating at a higher pace and allowing replacement of the damaged mucosa.[27] However, this usually results in mucosal hyperplasia, particularly in older pups, contributing to intestinal malabsorption and loss of fluids and electrolytes.[28] Immunocompetent mice shed MHV in high titers in feces but clear the infection within 3 to 4 wk;[25,30,35] however, several factors may influence the duration of infection, including the animal, genotype, and immune status of the mouse and the virus strain and route of infection.[25,27,31,32] Disease susceptibility varies among immunodeficient mice depending on the specific genetic defect.[28,37,196] Immune competent adult mice are susceptible to infection but do not normally show clinical disease.[196,197] Once the virus becomes enzootic in a mouse breeding colony, no clinical disease is seen because the newborn pups are protected from infection by colostral maternal antibodies; however, subclinical infection occurs as passive immunity declines after weaning.[26,195]

Polytropic strains of MHV have primary tropism for upper respiratory epithelium, where they initially replicate and then disseminate hematogenously to other tissues and organs, primarily, pulmonary vascular endothelium, with secondary

infection of hepatic, hemopoietic, and lymphoid tissues, causing acute necrosis and syncytia formation.[28,29,36] Neurotropic strains can migrate hematogenously or directly from the olfactory epithelium to the brain through olfactory neural pathways, causing necrotizing encephalitis that affects neurons, glia, and endothelium.[17,28,29,36] Surviving mice usually develop posterior paresis due to immune-mediated demyelination.[422] Polytropic strains of MHV spread by direct contact but are usually less contagious than are enterotropic strains. Vertical transmission can occur in some polytropic MHV strains but does not appear to be the main mode of transmission.[26] Like the enterotropic strains, disease outcome from polytropic strains depends on both host (genotype, age, and immune status) and viral factors (strain pathogenicity and tropism). In general, infant mice are more susceptible to severe disease, showing runting and neurologic signs, with reduced numbers weaned due to maternal cannibalism.[28] Enzootic infections are subclinical in immune-competent mice but immune-deficient mice, particularly T cell deficient mice, may show wasting, neurologic signs, and death.[29,197] Interferon-γ deficient mice may develop abdominal distention due to polyserositis.[156] Some MHV strains, such as JHM, contain an additional structural protein, hemagglutinin-esterase (HE), which binds sialic acids on surface glycoproteins and contains acetyl-esterase activity, enhancing viral S protein-mediated mucosal cell invasion and spread.[100] In contrast to MHV enterotropic strains, polytropic strains replicate in a wide variety of cells in vitro and can be a source of infection when injected into naïve mice.[293] MHV uses carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), a transmembrane glycoprotein that is expressed on epithelial, endothelial, and immune cells, as a virus cell receptor for attachment and invasion.[424] However, susceptibility to some MHV strains appears to be related to an allelic variation of CEACAM1. For example, a strain-specific allelic variant (*Ceacam1b*) in SJL/J mice makes this strain resistant to infection as compared with C57BL/6J and other mouse strains that express the *Ceacam1a* allele.[169,424] In addition, neurovirulent strains appear to use a different, yet to be determined, receptor-independent mechanism to infect neurons.[43,44,322] Some common polytropic MHV strains include MHV-1, MHV-2, MHV-3, MHV-JHM (MHV-4), MHV-A59, and MHV-S.[27,30-32,36,197] These polytropic viruses have been extensively studied as models of human neurologic diseases, hepatitis, and respiratory CoV infection.[111,120,232,239,386] Clinically, hepatic lesions caused by MHV infection result in elevated liver enzymes, affect protein synthesis, increase iron uptake, cause anemia, thrombocytopenia, leukopenia, pancytopenia, and increase monocyte procoagulant activity leading to thrombosis.[272,294] MHV causes marked immune modulation affecting both cell mediated and humoral responses.[96,104,371,453,461] In addition, mice infected with the neurotropic strain MHV-JHM display an increase in multiple chemotactic cytokines in the CNS (MCP-1, MCP-3, MIP-1, MIP-2, and RANTES); spinal cord astrocytes of chronically-infected mice express TNF-α, IL-1 β, and IL-6.[371,422] Astrocytes are considered to have a dual role in CNS pathophysiology, as they can both support regeneration and exert detrimental effects on surrounding cells and brain parenchyma.[6,205]

In infected colonies, mouse pups are initially protected by antibodies present in the colostrum of MHV-seropositive mothers, but the passive immunity lasts only 3 to 4 wk, after which the weanlings are susceptible to infection.[26,195-197] Mice that survive the infection and recover develop strain-specific immunity.[33,34] Genetically modified mice (that is, B cell-deficient mice, tumor necrosis factor knockout mice, and interferon-γ deficient mice) may shed MHV for prolonged duration and require rederivation of the affected colony using hysterectomy or embryo transfer.[93,196,345,366] Although MHV is considered a mouse specific pathogen, persistent infection promotes cross-species transmissibility by selection of MHV strains that recognize phylogenetic homologues of the normal MHV receptor.[23,190,191] Further supporting the potential cross-species transmissibility of *Murine coronavirus*, neurotropic MHV-JHM infected nonhuman primate brain tissue after peripheral inoculation.[62] Regarding the origin of MHV, a new species of *Betacoronavirus* (subgenus *Embecovirus*), isolated from *Rattus norvegicus* in China, *China Rattus coronavirus HKU24* (ChRCoV HKU24), is the parental strain of *Betacoronavirus-1;* interspecies transmission from rodents to other mammals occurred centuries ago, giving rise to human and bovine coronaviruses in the subgenus *Embecovirus*.[262]

Rat coronavirus (RCoV-P/SDAV). In 1970, an MHV variant, later named Parker's rat coronavirus (RCoV-P), was identified in a colony of research rats as the cause of respiratory epidemics in young rats.[344] Two years later, another coronavirus was described in rats that caused infection in the lower respiratory tract, eye, lacrimal glands, and salivary glands; it was called sialodacryoadenitis virus (SDAV).[51] Subsequent study revealed that RCoV-P can also cause sialodacryoadenitis, suggesting that RCoV-P and SDAV are most likely different strains of a coronavirus indigenous to rats.[355] Despite having different glycoproteins as cellular receptors, mice can be experimentally infected with SDAV and develop a similar disease to SDAV in rats, but natural SDAV disease in mice has not been reported.[50,159] Like MHV, rat coronavirus appears to have multiple strains.[94,95,237,299] The structural proteins of the rat coronaviruses, RCoV-P and SDAV, are closely related to those of MHV and are not divergent enough to be considered a new species. All 3 viruses appear to have the same parental strain, most likely the recently identified *China Rattus coronavirus HKU24* (ChRCoV HKU24) within the genus *Betacoronavirus* (subgenus *Embecovirus*).[24,163,245,262,459,498] Like other coronaviruses, RCoV is highly contagious with direct, aerosol, and fomite transmission causing epizootics in naïve rat populations.[50,94,158,247,293,344] Similar to MHV, genetics and age affect susceptibility to RCoV.[49,50,94,344,355] Primary tropism is to nasal respiratory epithelium, with secondary spread to lacrimal glands, salivary glands, and lungs.[48] Enzootic infections are usually inapparent or manifest as mild symptoms in very young rats.[344] Epizootics are characterized by respiratory signs or keratitis with corneal ulceration, conjunctivitis, porphyrin staining around the eyes, and cervical swelling due to edema around the submandibular salivary glands.[212,252] In both cases young rats are more susceptible to severe disease than are weanlings and older rats.[344,481] Mortality is unusual but can occur in newborn rats or when secondary opportunistic infections occur.[344] Microscopic changes include mild necrotizing rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, and multifocal pneumonitis with a mostly lymphocytic inflammatory response.[48,94,299,344,355,481] Recovered rats often show marked squamous metaplasia, more prominently in the Harderian glands.[293] Permanent eye damage can occur as a result of lesions affecting the lacrimal gland function and filtration angle of the eye (that is, keratitis sicca, corneal ulcerations, hyphema, and megaloglobus).[252,293] Recovered rats show short-lived immunity, with no cross-protection; reinfection with homologous rat coronaviruses can occur as early as 6 mo after the initial infection, with milder disease and less viral shedding than occurs after contact infection of virus-naïve controls.[356,465] Immune deficient rats become chronically infected, can shed virus for at least 10 wk, and may progress to wasting syndrome and die from

pneumonia.[182,466] Acute infection with SDAV is diagnosed based on clinical signs and lesions; however, respiratory tract lesions cannot be distinguished from those caused by Sendai virus.[281] SDAV infection strongly exacerbates *Mycoplasma pulmonis* disease, and RCoV infection enhanced nasal colonization with *Haemophilus influenzae* type B in infant rats.[311,393]

Guinea pig coronavirus. In 1990, typical coronavirus-like virions were reported in association with diarrhea, anorexia, and wasting in 3 to 4-wk-old guinea pigs.[210] Microscopically, the lesions were characterized by necrotizing enteritis with blunting and fusion of villi and syncytia that mostly affected the distal ileum.[210] Persistent excretion of coronavirus-like particles in guinea pigs was reported.[296] The prevalence of coronavirus-like virions in guinea pig colonies and its relationship to other coronaviruses is currently unknown, as is the cellular receptor the virus uses to attach and infect guinea pigs.[293]

Rabbit coronaviruses. *Rabbit enteric coronavirus (RECoV)*. Initially described in the early 1980s, Rabbit Enteric Coronavirus (RECoV) has not been fully characterized.[135,255,340,347] Analysis of structural polypeptides of the purified viral particles revealed a pattern similar to that of other coronaviruses, with the polypeptides cross reacting with 2 other coronavirus specific immune sera, avian IBV and porcine TGEV.[128] RECoV appears to have some antigenic relationship with the HCoV-229-E.[255]RECoV has been reported in commercial rabbitries and research colonies in Canada and Europe.[135,255,340,347] Serologic surveys suggest that RECoV is present in rabbitries in the United States with a prevalence ranging from 3% to 40%, with most seropositive rabbits being 4 mo of age or older.[124,135] RECoV usually causes transient mild diarrhea in young (3- to 8-wk-old) rabbits, although one study reported very high mortality.[127,135,340] In severe cases, rabbits can show lethargy, diarrhea, dehydration, emaciation, perineal fecal staining, and abdominal distention before dying.[135,255,340] Gross lesions are usually characterized by cecal distention with mucosal inflammation and edema; cecal contents are watery and colored white to tan.[135,255,340] The small and/or large intestines may also be affected.[135] Microscopically, the lesions are characterized by villous blunting with vacuolation and necrosis of intestinal epithelial cells along with mucosal edema and polymorphonuclear and mononuclear inflammatory infiltrates.[127,135,255,340] The virus shows tropism for gastrointestinal epithelium, but the cellular receptor is currently unknown. Rabbits acquire immunity as they age. The clinical signs of RECoV are not specific and should be differentiated from other causes of diarrhea in young rabbits (for example, coccidiosis, clostridiosis, colibacilosis, and rotavirus infection).[353] In 2012, a novel Betacoronavirus, rabbit coronavirus HKU14 (RbCoV HKU14), was isolated and characterized from fecal samples from domestic rabbits in animal markets in Guangzhou, China.[260] Molecular clock analysis using RNA-dependent RNA polymerase genes suggests that RbCoV HKU14 emerged relatively recently.[260] Its relationship to RECoV is currently unknown.

Rabbit pleural effusion disease/Infectious cardiomyopathy virus (PED/ICV). Pleural effusion disease/infectious cardiomyopathy virus (PED/ICV) was reported in Scandinavian countries in 1968 as a febrile illness causing deaths in rabbits inoculated with *Treponema pallidum*.[179,219] A viral origin was suspected, and the virus was described by electron microscopy in 1982 as a coronavirus.[179,340] PED/ICV was found as a contaminant in treponemal suspensions in laboratories in Europe, the United States, and Japan.[148] The viral gene sequence is unknown, but the available data suggest that it is an alphacoronavirus. PED/ICV is unlikely to be a natural pathogen of rabbits because it is only found in rabbits inoculated with contaminated stocks of *Treponema pallidum,* suggesting a different species, possibly human, as its origin.[340] PED/ICV is a multisystemic disease resembling some aspects of FIP with pathogenicity varying according to the isolate.[149] Clinical signs vary and may include fever, anorexia, weight loss, muscular weakness, tachypnea, iridocyclitis, circulatory compromise, and death.[88,149,150,152,340,402] Infected rabbits can show transient lymphopenia and hypoalbuminemia, heterophilia, and increased serum levels of potassium, lactate dehydrogenase, and γ-globulin.[150] Necropsy findings depend on the stage of the disease; the acute phase may include pleural effusion, lung edema, and right ventricular dilatation, while rabbits surviving the first week may have ascites and subepicardial and subendocardial hemorrhages.[150,340] Microscopic findings include multifocal myocardial degeneration and necrosis with little or no inflammatory response, hepatic focal necrosis, hepatosplenomegaly, lymphoid depletion of splenic follicles, lymph node depletion or reactive hyperplasia, depletion and focal degenerative changes of the thymus, mild proliferative changes in glomerular tufts, and mild anterior uveitis.[88,150,152,340,402] The cellular receptor used by PED/ICV is currently unknown.

Nonhuman primate coronavirus. Coronavirus-like particles in nonhuman primate fecal samples were first reported in 1979.[69] Coronavirus-like particles have been reported in both normal and diarrheal stool samples from chimpanzees, baboons, macaques, and marmosets.[377,404,462] The virus or viruses have not been isolated and lack characterization. Infection prevalence of up to 43% was reported in a large NHP colony with a prevalence of 49% in animals with diarrhea and 38% in those with normal feces.[404] Infection prevalence appears to be higher in older animals, and rarely affects nonweaned monkeys, suggesting colostral protection against infection and the fecal-oral route of infection.[404] Fecal viral excretion appears to persist after weaning.[69,404] Immunoblotting studies done on serum from marmosets with coronavirus-like particles and diarrhea suggest the virus is antigenically related to bovine enteric coronavirus but not the porcine transmissible gastroenteritis virus.[377] The cellular receptor used by the virus to attach to and infect nonhuman primates is unknown.

Coronaviruses of Wild Animals

All known human CoVs originated in animals,[257] with bats and birds believed to be the ancestral hosts for all CoVs.[174,203,257,427] The natural reservoir of the SARS-related CoV and the most likely origin for the 2002 SARS-CoV outbreak was the horseshoe bat (*Rhinolophus* spp.).[257,451] While the natural reservoir for the SARS-CoV-2 has not been formally identified, the genome sequence of the virus is most closely related to bat coronaviruses.[335,397,510] While bats are considered the natural reservoir for most alpha- and beta-coronaviruses, other mammals usually act as intermediate hosts before eventually infecting humans. In the 2002 SARS-CoV outbreak, the Himalayan palm civet (*Paguma larvata*) was identified as the primary, intermediate host for the virus between bats and humans.[131,178,278] The intermediate mammalian host for SARS-CoV-2 was initially thought to be the Malayan pangolin (*Manis javanica*) due to sequence similarity in coronaviral isolates from captive pangolins;[253,285] however, more recent analysis has questioned this determination.[463] Ferrets and cats are highly susceptible to SARS-CoV-2 [via experimental infection];[297] whereas dogs have low susceptibility, and pigs, chickens, and ducks are not susceptible to the virus.[397] SARS-CoV2 has been transmitted from humans to farmed mink in the Netherlands and back to humans.[339,341] SARS-CoV isolated from humans can infect and

be transmitted by domestic cats and ferrets; however, these animals can also clear the infection.[278] The porcine CoV, TGEV, and canine and feline CoVs can cross-infect pigs, dogs, and cats with varying disease phenotypes and levels of cross-protection in the heterologous host.[236,381,382] Several BCoVs or bovine-like CoVs were identified as pathogens of enteric and/or respiratory diseases in ruminants, dogs, birds, and even humans.[7,11]

The capture, farming, and trade of wild animals are suspected to be major contributors to the emergence and spread of coronaviruses to humans, especially SARS-CoV and SARS-CoV-2.[203,487] The stress of poor nutrition and overcrowded conditions lowers their immune competence and makes them more susceptible to infections. These factors also result in increased shedding of coronaviruses by infected animals around human habitation and along the supply chain for human consumption.[203,487] In the 2002 SARS-CoV outbreak, captive, Himalayan palm civets (*Paguma larvata*) at Chinese wet markets tested positive for SARS-CoV, with some developing respiratory disease; whereas, palm civets in the wild were negative.[278] Evidence of SARS-CoV-like infections has also been observed in many other marketed species, including the cat (*Felis catus*), the red fox (*Vulpes vulpes*), and the Chinese ferret badger (*Melogale moschata*).[278] Farms that raise wild species are abundant in Asia, with over 6,000 registered wildlife farms in Vietnam in 2014 holding over 1 million animals.[203] In Vietnam, 34% of wild, captive, field rats (*Rattus* spp. and *Bandicota* spp.) and 75% of insectivorous bats in guano farms were PCR-positive for coronaviruses.[203]

As discussed in the previous section on domestic animals, coronaviruses can significantly affect domestic agricultural species. BCoVs cause significant respiratory and enteric disease in cows and other domestic ruminants and are also an important pathogen in a wide variety of captive and free-range wild ruminants around the world (Figure 4). Most of the viruses isolated from wild ruminants are biologically and genetically similar to BCoV and are often called bovine-like CoVs.[11]

Most cases of CoV disease in wild ruminants have been reported in wild animal parks around the world and include dromedary camels (*Camelus dromedarius*) in Wisconsin, giraffes (*Giraffa camelopardalis*) in Ohio, and musk oxen (*Ovibox moschatus*) in England.[11] Most reports of disease in wild ruminants have involved the gastrointestinal tract. A survey of free-roaming deer found that 7% of the white-tailed deer (*Odocoileus virginianus*) in Ohio and 9% of the mule deer (*Odocoileus hemionus*) in Wyoming were seropositive for antibodies to BCoV.[382] SARS-CoV-2 also infects white-tailed deer, presumably binding to their ACE2 receptor,[109] and could be an important reservoir host in the United States.[97,183,243]

FCoVs have been widely reported in both domestic and wild cats. Most cases of FCoV cause mild enteric disease, termed feline enteric coronavirus (FECV); however, feline infectious peritonitis (FIP) is caused by a rare but highly lethal "mutant" form of FECV (FIPV) that can be found in approximately 10% of domestic or feral cats that are seropositive for FCV.[59,73] The cheetah (*Acinonyx jubatus*) is especially sensitive to FIPV.[142,417] FIP has also been reported in a wild mountain lion (*Puma concolor*) in California.[411] FCoVs were detected in numerous captive Felidae species in zoological parks in the United States (Figure 5). As stated before, the Himalayan palm civet (*Paguma larvata*) was found to be the intermediate host for SARS-CoV.[278] CoV has been detected in Asian leopard cats (*Prionailurus bengalensis*) in Chinese wet markets.[131] In 2020, multiple large cats, including a Malayan tiger (*Panthera tigris jacksoni)*, 2 Siberian tigers (*Panthera tigris tigris*), and 3 African lions (*Panthera leo*), at the Bronx Zoo tested positive for SARS-CoV-2. All were reported to have developed a dry cough.[271] In addition, 9 Asiatic lions (*Panthera leo persica*) tested positive for the SARS-CoV-2 B.1.617.2

Common Name	Species	Country	# Positive/ # Tested	% Positive
Caribou/Reindeer	*Rangifer tarandus*	Canada	4/58	6.9
Elk/Wapiti	*Cervus elephus*	Canada	5/11	45.5
Elk/Wapiti	*Cervus elephus*	USA (Kansas)	2/2	100
Samber deer	*Cervus unicolor*	USA (Ohio)	3/3	100
White-tailed deer	*Odocoileus virginianus*	USA (Ohio)	3/3	100
Sika deer	*Cervus nippon*	Japan	2/179	1.1
Water deer	*Hydropotes inermis*	South Korea	3/77	3.9
Musk oxen	*Ovibus moschatus*	UK	ND	ND
Wisent	*Bison bonasus*	South Korea	1/4	25
Wood bison	*Bison bison athabascae*	Canada	2/31	7
Water buck	*Kobus ellipsiprymnus*	UK	9/9	100
Water buck	*Kobus ellipsiprymnus*	USA (Ohio)	1/1	100
Sitatunga	*Tragelaphus spekei*	UK	ND	ND
Sitatunga	*Tragelaphus spekei*	South Korea	1/3	33.3
Stable antelope	*Hippotragus niger*	USA (Ohio)	1/1	100
Nyala	*Tragelaphus angasii*	South Korea	1/2	50
Giraffe	*Giraffa camelopardalis*	USA (Ohio)	3/3	100
Himalayan tahr	*Hemitragus jemlahicus*	South Korea	2/3	66.7

Figure 4. Bovine-like Coronaviruses reported in captive or free-range, wild ruminants between 1981–2019. ND: not defined. Adapted from reference 11.

Common Name	Species	Clinical presentation
Cheetah	*Acinonyx jubatus*	Healthy
Bobcat	*Lynx rufus*	No data
Bobcat	*Lynx rufus*	No data
Cheetah	*Acinonyx jubatus*	FIP
Cheetah	*Acinonyx jubatus*	Healthy
Cheetah	*Acinonyx jubatus*	Healthy
Siberian tiger	*Panthera tigris altaica*	Healthy
Cheetah	*Acinonyx jubatus*	Chronic diarrhea
Lynx	*Lynx canadensis*	Healthy
African lion	*Panthera leo*	No data
Jaguar	*Panthera onca*	Healthy
Jaguar	*Panthera onca*	Healthy
Cheetah	*Acinonyx jubatus*	Weight loss, decreased appetite
Snow leopard	*Panthera uncia*	Healthy
Cheetah	*Acinonyx jubatus*	Healthy
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea
Cheetah	*Acinonyx jubatus*	Necrotizing colitis/diarrhea

Figure 5. Feline Coronavirus reported in US captive wild cats (2002). Adapted from reference 229.

(Delta variant) at a zoological park in Chennai, India, with 4 developing acute respiratory signs, 3 of which died.[319]

Canine coronavirus has most often been associated with mild enteric disease,[430] but some strains have caused severe respiratory disease[139,362] or lethal systemic disease in domestic canines.[61] Reports of disease in wild canines are sparse. Coyotes (*Canis latrans*) with enteritis are often found to be infected with both canine parvovirus and CCoV.[502] In 1985, 61% of the captive coyotes maintained at a U.S. Sheep Experiment Station in Idaho had antibodies to CCoV,[154] and 70% (167/240) of wolves (*Canis lupus*) captured during spring in Alaska between 1994 to 1999 tested positive for CCoV antibodies[502]

Swine coronaviruses can be found in wild or feral swine populations and are believed to provide a reservoir for domestic swine exposures.[310] The feral swine population in the United States is estimated at approximately 5 to 6 million.[47] Between 2012 to 2015, approximately 8,000 feral swine were tested for CoV in the United States, with 253 (3%) testing positive for either PEDV or TGEV.[47]

Avian coronaviruses fall into the *Deltacoronavirus* or *Gammacoronavirus* genera and are known to infect numerous domestic and wild birds. Avian coronaviruses have been found in wild birds on every continent.[78] Several CoVs, including the most economically important, avian CoV, IBV, have been detected in healthy wild birds, which are believed to serve as a reservoir for domestic birds.[89,314] Gammacoronaviruses are found predominantly in Anseriformes birds (waterfowl, for example, geese, ducks, and swans), whereas Deltacoronaviruses have been detected in Ciconiiformes (storklike), Pelecaniformes (medium to large water birds), and Anseriformes birds.[89] A list of coronaviruses isolated from wild birds is presented in Figure 6.

While most mammalian coronaviruses are classified into the *Alphacoronavirus* and *Betacoronavirus* genera, a few fall into the *Gammacoronavirus* (captive Beluga whale: *Delphinapterus leucas;* and Bottlenose dolphins:*Tursiops aduncus* and *T. truncatus*)[312,457,485] and *Deltacoronavirus* (Asian leopard cat: *Prionailurus bengalensis*)[131] genera.

Diagnosis and Treatment of Coronaviral Diseases

Currently reverse transcriptase polymerase chain reaction (RT-PCR), using clinical samples, is the most commonly used method for diagnosis of active infection, particularly in well characterized CoVs, like domestic fowl, canine, feline, swine, bovine, equine, ferret, alpaca, mouse, rat, and human coronaviruses.[92] Serologic assays like, enzyme linked immunosorbent assay (ELISA), immunofluorescence (IF), and serum neutralization tests are used to test for prior exposure, and IF and immunohistochemistry (IHC) are used for detection of viral antigens in affected tissues.[71] Virus culture and isolation are used to confirm diagnosis and electron microscopy (EM) is used to demonstrate characteristic virus morphology in clinical samples after ruling out other diseases that can cause similar clinical signs.[106,195,304,418,449] EM is more often used in less studied/characterized coronaviruses like guinea pig, rabbit, and nonhuman primate coronaviruses.[347,353]

This section provides examples of the diagnostic methods used to detect and diagnose CoVs in some of the different species. For felines, diagnosis of FIP is based on a combination of signalment, history, clinical signs, and clinical assays along with RT-PCR and IHC in clinical samples.[230] In the case of swine coronaviruses, diagnosis of the specific virus causing SECD can be complicated because CoV coinfections can occur in swine. TGEV diagnosis can be made by IF, IHC, ELISA, and virus isolation, but these methods do not differentiate TGEV

Common Name	Avian Order	Species
Gray teal	*Anseriformes*	*Anas gracilis*
Pacific black duck		*Anas superciliosa*
Radjah shelduck		*Tadorna radjah*
Australian wood duck		*Chenonetta jubata*
Australian shelduck		*Tadorna tadornoides*
Common teal		*Anas crecca*
Chestnut teal		*Anas castanea*
Northern shoveler		*Anas clypeata*
Eurasian wigeon		*Anas penelope*
Northern pintail		*Anas acuta*
American wigeon		*Anas americana*
Mallard duck		*Anas platyrhynchos*
Lesser whistling duck		*Dendrocygna javanica*
Tufted duck		*Aythya fuligula*
Swan		*Cygnus olor*
Greylag Goose		*Anser anser*
Pied heron	*Pelecaniformes*	*Ardea picata*
Pond heron		*Ardeola bacchus/speciosa*
Gray heron		*Ardea cinerea*
Night heron		*Nycticorax nycticorax*
Black-faced spoonbill		*Platalea minor*
Curlew sandpiper	*Charadriiformes*	*Calidris ferruginea*
Red-necked stint		*Calidris ruficolis*
Sharp-tailed sandpiper		*Calidris acuminata*
Ruddy turnstone		*Arenaria interpres*
Short-tailed shearwater	*Procellariiformes*	*Ardenna tenuirostris*
Black kite	*Acciptriformes*	*Milvus migrans*
Spotted turtle dove	*Columbiformes*	*Streptopelia chinensis*
Common pigeon		*Columba livia*
Little Raven	*Passeriformes*	*Corvus mellori*
Great kiskadee		*Pitangus sulphuratus*
Red-ruffed fruitcrow		*Pyroderus scutatus*
Ruddy-breasted crake	*Gruiformes*	*Porzana fusca*
Great cormorant	*Suliformes*	*Phalacrocorax carbo*
Black-headed Gull	*Charadriiformes*	*Larus ridibundus*
Common pheasant	*Galliformes*	*Phasianus colchicus*
Orange-winged amazon parrot	*Psittaciformes*	*Amazona amazonica*
Blue-and-gold macaw		*Ara ararauna*
Plain parakeet		*Brotogeris tirica*
Striped owl	*Strigiformes*	*Asio clamator*
Tropical screech owl		*Megascops choliba*
Campo flicker	*Piciformes*	*Colaptes campestris*
Black vulture	*Cathartiformes*	*Coragyps atratus*
Roadside hawk	*Accipitriformes*	*Rupornis magnirostris*

Figure 6. Avian Coronaviruses reported in wild birds. Adapted from references 78, 89, and 134.

from PRCoV.[293] ELISA using monoclonal antibodies against the TGEV peplomer and RT-PCR using specific primers can be used to detect and differentiate TGEV from PRCoV.[63,489] PEDV diagnosis can be confirmed by virus isolation in primary porcine cell culture or in Vero cells with added trypsin, or IF or IHC to detect viral antigens in affected tissues, or RT-PCR molecular

assays using clinical samples, or serologic assays like ELISA to monitor for prior exposure by demonstration of antibodies in convalescent animals.[129] SeCoV-infected pigs seroconvert against PEDV but test negative in a TGEV-specific ELISA that detects antibodies against the S protein. Specific detection of the chimeric SeCoVs either requires the development of a new diagnostic RT-qPCR assay or the combined use of assays targeting the PEDV S-gene and another part of the TGEV genome.[41] PDCoV diagnosis can be made using virus culture and isolation and observation of the cytopathic effect, and with IF, IHC, ELISA, and RT-PCR.[504] RT-PCR based tests have been designed to diagnose SADS-CoV.[342,509] An indirect ELISA to detect IgG antibodies using a recombinant plasmid that expresses the spike protein of SADS-CoV was recently reported.[349] PRCoV diagnosis is made by virus isolation or RT-PCR testing of nasal swabs or tissue samples collected from the trachea and lungs, with specific primers used to differentiate it from TGEV.[234] In addition, IF, IHC, and ELISA, using monoclonal antibodies to detect PRCoV antigen in specimens, is preferred over serology due to crossreactivity with TGEV.[401] Because the disease is usually mild and recovered pigs are resistant to TGEV, little effort has been made to develop specific treatments or vaccines to prevent the disease.[293] MCoV cross react with pig TGEV and PEDV on serologic assays.[172] PED/ICV cross react with several alphacoronaviruses in serologic assays, including HCoV-229E, FIPV, CCoV, and swine TGEV.[402,403]

Currently, specific treatments are not available for CoVs that affect companion and farm animals but active research is ongoing.[209,230] When vaccines are available, they will provide only partial protection because immunity is strain-specific and CoVs are known for their high mutation rates and frequent recombination.[52,354] Primary medical management is supportive and includes treatments for fluid and electrolyte balance, resolution of severe leukopenia, systemic inflammation, and metabolic disturbances.[46,369] In the case of ferret systemic coronavirus, immune suppressive drugs may slow down disease progression.[327] Two approaches are available for FIP. As FIP is an immune-mediated disease, the first treatment approach is to modulate the immune response using drugs such as corticosteroids. This is a palliative treatment, with cats surviving weeks or months.[209,230] Cytokines have also been used to modulate the immune response with limited success and higher survival rates in cats with the dry form of FIP.[230] The second approach is to use experimental antiviral compounds to inhibit FCoV replication by targeting proteases necessary for viral protein cleavage.[230,303]

Control measures for CoVs include strict sanitation and management practices to eliminate the virus from the environment and prevent reintroduction because animal populations may clear the virus with time if new introductions are avoided.[414] For example, spread of MHV can be prevented by temporary cessation of breeding and avoiding the introduction of MHV-naive mice.

Extensive research during the COVID-19 pandemic has resulted in the United States Food and Drug Administration (FDA) approval of the first antiviral drug, remdesivir (Veklury), specific for the treatment of COVID-19 patients. Remdesivir may be prescribed for people who are hospitalized with COVID-19 and need supplemental oxygen or have a higher risk of serious illness. In addition, the FDA has given emergency use authorization to several drugs that have antiviral and/or antiinflammatory properties (Paxlovid, Molnupiravir, Baricitinib, and Tocilizumab), monoclonal antibodies (Sotrovimab, Evusheld, and Bebtelovimab), and convalescent immune plasma to treat and/or prevent COVID-19 infection.[443]

Coronaviral Vaccines

The 2019 SARS-CoV-2 pandemic spurred the most rapid vaccine development in history. Prior to 2020, the average timeline for vaccine development was 5 to 10 y.[218] However, within 9 mo of the World Health Organization declaring SARS-CoV-2 a worldwide pandemic (March 2020), 3 vaccines were approved for emergency use in humans [Sputnick V – Gam-COVID-Vac,[287] Moderna mRNA-1273,[444] and Pfizer BNT162b2[445]]. As of September 2021, 8 SARS-CoV-2 vaccines are currently in use worldwide.[491] Significant research into human coronaviral vaccines took place with the outbreak of SARS-CoV in 2003 and MERS-CoV in 2008, with some going to phase 1 clinical trials; however, vaccines for coronaviral diseases of animals have been used for over 50 y and played an important role in our understanding of mammalian and avian immune responses to coronaviruses.

Coronavirus vaccines for chickens. Infectious Bronchitis Virus (IBV) is a major disease of domestic chickens (*Gallus gallus domesticus*) and causes significant morbidity and mortality and economic losses.[72,433] Vaccines have been used against IBV since the 1960s, and before 2020 were the only licensed vaccines targeting respiratory coronaviral diseases.[70,383] Hundreds of IBV serotypes (or strains) have been isolated, with the majority of differences occurring in the S1 subunit of the spike protein, which is the primary inducer of protective immunity.[181] As such, vaccines used worldwide usually contain one or more variants affecting that specific region. For example, vaccines used in North America most often target the Massachusetts (M41), Arkansas, and Connecticut strains; vaccines in Europe most often cover the 4/91 and D274 strains; and vaccines in China target the QX strain.[433] Newborn chicks are usually vaccinated at one day of age with a live attenuated vaccine via a course spray. Meat-producing chickens usually only receive the single dose; whereas birds for breeding and egg production will receive multiple doses at 2, 4, and 6 wk of age.[433] Currently, over 80 USDA-licensed vaccines are available against IBV, with most containing multiple serotypes and used in combination with other viral vaccines and bacterin components (Figure 7).

Coronaviral vaccines for canines. Two separate coronaviruses cause mild enteric [Alphacoronavirus (CCoV-1)] or respiratory [Betacoronavirus (CRCoV)] disease in dogs. Commercially available inactivated and modified-live vaccines are available for the enterotropic but not the respiratory virus[433] (Figure 8). Vaccination protects from disease but not from infection, and virus can be shed in the feces.[433] The American Animal Hospital Association (AHAA) currently does not recommend canine coronaviral vaccinations because infection: (1) causes mild or subclinical disease, (2) generally occurs in dogs 6 wk of age and younger, and (3) is typically self-limiting.[153]

Coronaviral vaccines for felines. FCoV infections generally cause subclinical or mild enteric disease. FIP is a lethal form of FECV that arises from an enhanced immunologic response in a subset of cats. Only one USDA-licensed vaccine (FeloCell FIP - Zoetis) is currently available against FIPV (Figure 9). The vaccine is an attenuated, temperature-sensitive strain for intranasal administration in healthy cats 16 wk of age or older. The manufacturer states that the attenuated strain can replicate only in the respiratory tract and cannot spread systemically. The AHAA does not recommend vaccination of pet cats for FIP "because of its questionable ability to uniformly prevent disease in North American cat populations."[415] Only FCoV-seronegative

Product	Product Type	Product Form	Manufacturer
Bronchitis Vaccine	Vaccine	Ark Type, Live Virus	Biomune Company
		Ark Type, Live Virus	Zoetis Biomune Company
		Ark Type, Live Virus	Boehringer Ingelheim Animal Health USA Elanco US
		Ark Type, Live Virus	Boehringer Ingelheim Animal Health USA Intervet
		Conn Type, Live Virus	Boehringer Ingelheim Animal Health USA
		Delaware Type, Modified	Intervet (Merck)
		Georgia Type, Live Virus	Intervet (Merck) Zoetis Biomune Company
		Georgia Type, Live Virus	Intervet (Merck) Zoetis Biomune Company
		Mass and Ark Types, Live Virus	Zoetis Biomune Company
		Mass and Ark Types, Live Virus	Biomune Company
		Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis Biomune Company
		Mass and Conn Types, Live Virus	Biomune Company
		Mass and Conn Types, Live Virus	Intervet (Merck)
		Mass Type, Killed Virus	Elanco US Biomune Company
		Mass Type, Live Virus	Zoetis Biomune Company
		Mass Type, Live Virus	Elanco US Biomune Company
		Mass Type, Live Virus	Intervet (Merck)
		Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA
		Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA
		Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA
Bursal Disease-Newcastle Disease-Bronchitis Vaccine	Vaccine	B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA
		Mass Type, Killed Virus	Zoetis
		Standard and Variant, Mass and Ark Types, Killed Virus	Boehringer Ingelheim Animal Health USA
Bursal Disease-Newcastle Disease-Bronchitis-Reovirus Vaccine	Vaccine	Killed Virus	Zoetis
		Mass Type, Killed Virus	Biomune Company
		Mass Type, Killed Virus	Zoetis
		Mass Type, Killed Virus	Zoetis Elanco US
		Mass Type, Killed Virus	Boehringer Ingelheim Animal Health USA

Figure 7. USDA-Licensed chicken coronaviral vaccines. (*Continued*)

			Elanco US
		Standard and Variant, Mass and Ark Types, Killed Virus	Elanco US
		Standard and Variant, Mass Type, Killed Virus	Intervet (Merck) Elanco US Biomune Company
		Standard and Variant, Mass Type, Killed Virus	Boehringer Ingelheim Animal Health USA
		Standard and Variant, Mass Type, Killed Virus	Zoetis Biomune Company
Newcastle-Bronchitis Vaccine	Vaccine	B1 Type, B1 Strain, Mass and Ark Types, Live Virus	Intervet (Merck)
		B1 Type, B1 Strain, Mass and Ark Types, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis
		B1 Type, B1 Strain, Mass and Ark Types, Live Virus	Boehringer Ingelheim Animal Health USA
		B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis
		B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Elanco US
		B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA
		B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA
		B1 Type, B1 Strain, Mass and Conn Types, Live Virus	Intervet (Merck)
		B1 Type, B1 Strain, Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis
		B1 Type, B1 Strain, Mass Type, Live Virus	Elanco US
		B1 Type, B1 Strain, Mass Type, Live Virus	Zoetis
		B1 Type, B1 Strain, Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA
		B1 Type, C2 Strain, Mass and Conn Types, Live Virus	Intervet (Merck)
		B1 Type, C2 Strain, Mass Type, Live Virus	Intervet (Merck)
		B1 Type, LaSota Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA
		B1 Type, LaSota Strain, Mass and Conn Types, Live Virus	Intervet (Merck)
		B1 Type, LaSota Strain, Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis
		B1 Type, LaSota Strain, Mass Type, Live Virus	Boehringer Ingelheim Animal Health USA Zoetis
		B1 Type, LaSota Strain, Mass Type, Live Virus	Elanco US
		Mass and Ark Types, Killed Virus	Boehringer Ingelheim Animal Health USA
		Mass Type, Killed Virus	Biomune Company
		Mass Type, Killed Virus	Zoetis

Figure 7. (Continued)

Newcastle Disease-Bronchitis Vaccine-Salmonella enteritidis Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Mass Type, Killed Virus	Elanco US
		VG/GA Strain, Mass and Conn Types, Live Virus	Boehringer Ingelheim Animal Health USA
		Mass and Ark Types, Killed Virus	Elanco US
		Mass and Ark Types, Killed Virus	Elanco US
Newcastle-Bronchitis Vaccine-Mycoplasma Gallisepticum Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Mass Type, Killed Virus	Elanco US
Newcastle-Bronchitis Vaccine-Salmonella enteritidis Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Mass Type, Killed Virus	Intervet (Merck) Zoetis Biomune Company
Bronchitis Virus	For further manufacture: vaccines[1]	Mass Type, Killed Virus	Biomune Company

[1]For Further Manufacture - These products represent one or more biologic fractions brought to a prescribed stage of production requiring further processing before becoming a completed or finished product.

Figure 7. (Continued)

cats can receive the vaccine, and most cats born in environments with a high incidence of FCoV become infected prior to 16 wks of age, making vaccination ineffective.[388]

Coronaviral vaccines for swine. Six known CoVs cause gastrointestinal or respiratory disease in swine, including the alphacoronaviruses TGEV, PRCoV, PEDV, and SADS-CoV; the betacoronavirus, PHEV; and the deltacoronavirus, PDCoV.[433] To date, vaccines have been developed only for TGEV and PEDV.

Several vaccines have been developed worldwide against TGEV. Two USDA- licensed TGEV vaccines are currently available in the United States (Figure 10). Both contain a modified-live TGEV in combination with a modified-live rotavirus. One of these vaccines also contains *Clostridium perfringens* Type C toxoid and *Escherichia coli* bacterin components. Because suckling pigs (1 to 2 wk of age) are the most TGEV-susceptible population and vaccination of sucklings does not provide the protective immunity during the susceptible window for disease, vaccines are used in pregnant sows that in turn provide protective antibodies to sucklings via passive transfer in the milk.[165,383] The vaccine is given to pregnant sows/gilts via both intranasal and intramuscular routes, usually about 2 to 4 wk before farrowing. PRCoV arose as an S protein variant of TGEV with tropism for the respiratory epithelium but shares many epitopes of TGEV. Respiratory disease from PRCoV is generally mild, and neutralizing antibodies to PRCoV cross react with TGEV and have dramatically reduced TGEV outbreaks.[395] Therefore, PRCoV is considered a natural "vaccine" against TGEV, and little effort has been made to develop specific treatments or vaccines to prevent the disease.[395]

Numerous vaccines have also been developed worldwide against PEDV.[165] Two USDA-licensed vaccines for PEDV are currently available: a killed virus (Zoetis) and an RNA particle platform vaccine [Intervet (Harrisvaccines) – MERCK] (Figure 10). As with TGEV, the highest mortality from PEDV occurs in suckling piglets, 1 to 2 wk of age. Therefore, vaccination of pregnant sows to provide lactogenic passive immunity is the regimen currently used.

Coronaviral vaccines for bovines. Bovine coronaviral diseases most often cause severe diarrhea in newborn calves, 'winter dysentery' in adult cows, or an infectious respiratory disease ('shipping fever') in cows of all ages.[384] As with the swine enteric coronaviral diseases, the most susceptible population to enteric disease is newborn calves, and vaccination of pregnant cows prior to calving and lactogenic transfer of neutralizing antibodies is the primary method for protection against calf diarrhea.[433] Oral and intranasal vaccines against neonatal calf diarrhea are also available for newborn calves. While many of the vaccines report protection against severe disease, their efficacy is been questionable because immunity does not prevent reinfection or viral shedding.[79,87,137] A list of current USDA-licensed BCoV vaccines is provided in Figure 11. While no licensed vaccines are available for BCoV respiratory disease, the intranasal administration of a modified live virus vaccine against the enteric BCoVs seems to provide some protection.[118] A commercially available BCoV vaccine induces modest antibody titers against ECoV in horses; however, challenge studies have not been performed to determine whether the generated antibodies will protect against ECoV.[330,365]

Coronaviral vaccines for mustelids. Domestic ferrets (*Mustela putorius furo*) and mink (European: *Mustela lutreola* and American: *Neovison vison*) are highly susceptible to infections with human coronaviruses including SARS-CoV and SARS-CoV-2.[90,238,323,378,396] Since the start of the COVID-19 pandemic, numerous reports have appeared of SARS-CoV-2 infections

Product	Product Type	Product Form	Manufacturer
Canine Coronavirus Vaccine	Vaccine	Killed Virus	Boehringer Ingelheim Animal Health USA* Intervet (Merck) Zoetis Elanco US
		Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
		Modified Live Virus	Boehringer Ingelheim Animal Health USA
Canine Coronavirus-Parvovirus Vaccine	Vaccine	Modified Live and Killed Virus	Zoetis
		Modified Live and Killed Virus	Elanco US
		Modified Live Virus	Boehringer Ingelheim Animal Health USA
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine	Vaccine	Modified Live and Killed Virus	Intervet (Merck)
		Modified Live and Killed Virus	Zoetis
		Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
		Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
		Modified Live Virus	Boehringer Ingelheim Animal Health USA
Canine Coronavirus Vaccine-Borrelia Burgdorferi Bacterin-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Coronavirus Vaccine-Borrelia Burgdorferi Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Elanco US
Canine Coronavirus Vaccine-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Coronavirus Vaccine-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Coronavirus Vaccine-Leptospira Icterohaemorrhagiae Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Boehringer Ingelheim Animal Health USA
Canine Coronavirus Vaccine-Leptospira Icterohaemorrhagiae Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Boehringer Ingelheim Animal Health USA Elanco US
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Borrelia Burgdorferi Bacterin-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Borrelia Burgdorferi Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Elanco US

Figure 8. USDA-Licensed canine coronaviral vaccines.

in farmed and feral mink and passage of SARS-CoV-2 from captive mink to humans.[238,339,341,400] While no coronavirus vaccines are currently licensed for pet ferrets or farmed mink, the US Department of Agriculture (USDA) Center for Veterinary Biologics issued a notice in November 2020 calling for product license and permit applications for vaccines against SARS-CoV-2 in mink. Two United States companies (Zoetis and Medgene Labs) are currently developing mink coronaviral vaccines for USDA licensure.[173] While SARS-CoV-2 infection has not been reported in the endangered, black-footed ferret (*Mustela nigripes*), the US Geological Survey (USGS) under the authority of the Fish and Wildlife Services (USFWS) is testing a SARS-CoV-2 vaccine in a small population of captive black-footed ferrets.[267]

Vaccine-associated Disease Enhancement

The mammalian immunologic response to viral infections results from a combination of the innate and adaptive immune systems with the goal of clearing the virus. These immune responses often lead to host tissue destruction at the site of infection and in some cases can exacerbate the disease, as reported for human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), hepatitis-B virus (HBV), hepatitis-C virus (HCV), and possibly SARS-CoV and SARS-CoV-2 infections in humans.[269,358] One mechanism by which this can occur is antibody-dependent enhancement (ADE) of viral infectivity, in which the uptake of antibody bound viruses by macrophages allows their enhanced replication and dissemination. ADE is one of the primary mechanisms behind the pathogenesis of FIP.[269,358] Vaccine-associated disease enhancement (VADE) has been reported for numerous viral vaccines and is associated with both ADE and immunopathological responses of Type 2 T helper cells.[419] VADE has been reported with the FIP vaccine,[358] PEDV,[499] and experimental vaccines in mouse models of SARS-CoV.[438]

Conclusion

Many species of domestic and wild animals carry CoVs, with some known to carry beta-CoVs closely related to SARS-CoV, MERS, and SARS-CoV-2 and some having a wide geographic distribution in nature. With continued human population expansion, resulting in closer contact with animal ecosystems, an increased risk of virus spillover from animals to people is illustrated by the increased frequency of viral disease outbreaks of zoonotic origin in the last 20 y. Wild animal trade for human consumption and the exotic pet industry create high-risk situations for cross-species transmission of CoVs and other potential zoonotic pathogens. Captive wild animals may show increased susceptibility to infections due to immune suppression secondary to capture stress, poor husbandry and overcrowded conditions in unregulated "wet markets," creating the perfect opportunity for potential interspecies transmission of disease. In the case of coronaviruses, this situation provides an environment that supports the creation of new pathogens through mutations and recombination in the new host. Experience has shown that developing effective therapeutics and vaccines for

Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Zoetis
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Leptospira Canicola-Icterohaemorrhagiae Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Intervet (Merck)
		Modified Live and Killed Virus	Zoetis
		Modified Live Virus	Boehringer Ingelheim Animal Health USA
Canine Distemper-Adenovirus Type 2-Coronavirus-Parainfluenza-Parvovirus Vaccine-Leptospira Icterohaemorrhagiae Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA
		Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA Elanco US
		Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA
Canine Distemper-Adenovirus Type 2-Coronavirus-Parvovirus Vaccine-Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA* Elanco US
Canine Distemper-Adenovirus Type 2-Coronavirus-Parvovirus Vaccine-Leptospira Icterohaemorrhagiae Bacterial Extract	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA
		Modified Live and Killed Virus	Boehringer Ingelheim Animal Health USA Elanco US
*Conditional USDA License	9 CFR 102.6 - "In order to meet an emergency condition, limited market, local situation, or other special circumstance, including production solely for intrastate use under a State-operated program, the Administrator may, in response to an application submitted as specified in §102.3(b) of this part, issue a conditional U.S. Veterinary Biological Product License to an establishment under an expedited procedure which assures purity and safety, and a reasonable expectation of efficacy."		

Figure 8. (Continued)

Product	Product Type	Product Form	Manufacturer
Feline Infectious Peritonitis Vaccine	Vaccine	Modified Live Virus	Zoetis
Feline Infectious Peritonitis Virus	For further manufacture: vaccines[1]	Modified Live Virus	Zoetis
[1]For Further Manufacture - These products represent one or more biologic fractions brought to a prescribed stage of production requiring further processing before becoming a completed or finished product.			

Figure 9. USDA-Licensed feline coronaviral vaccines.

Product		Product Type	Product Form	Manufacturer
Porcine	Porcine Epidemic Diarrhea Vaccine	Vaccine	Killed Virus	Zoetis*
			RNA Particle Platform	Intervet (Merck)*
	Porcine Rotavirus-Transmissible Gastroenteritis Vaccine	Vaccine	Modified Live Virus	Intervet (Merck)
	Porcine Rotavirus-Transmissible Gastroenteritis Vaccine-Clostridium Perfringens Type C-Escherichia coli Bacterin-Toxoid	Vaccines with bacterins/bacterial extracts/toxoids	Modified Live Virus	Intervet (Merck)
*Conditional USDA License	9 CFR 102.6 - "In order to meet an emergency condition, limited market, local situation, or other special circumstance, including production solely for intrastate use under a State-operated program, the Administrator may, in response to an application submitted as specified in §102.3(b) of this part, issue a conditional U.S. Veterinary Biological Product License to an establishment under an expedited procedure which assures purity and safety, and a reasonable expectation of efficacy."			

Figure 10. USDA-Licensed porcine coronaviral vaccines.

Product	Product Type	Product Form	Manufacturer
Bovine Coronavirus Vaccine	Vaccine	Modified Live Virus	Intervet (Merck)
Bovine Rotavirus-Coronavirus Vaccine	Vaccine	Killed Virus	Elanco US
		Modified Live Virus	Zoetis
Bovine Rotavirus-Coronavirus Vaccine-Clostridium Perfringens Type C-Escherichia coli Bacterin-Toxoid	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Elanco US
		Killed Virus	Zoetis
Bovine Rotavirus-Coronavirus Vaccine-Clostridium Perfringens Types C and D-Escherichia coli Bacterin-Toxoid	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Intervet (Merck)
Bovine Rotavirus-Coronavirus Vaccine-Escherichia coli Bacterin	Vaccines with bacterins/bacterial extracts/toxoids	Killed Virus	Zoetis
Bovine Coronavirus	For further manufacture: vaccines[1]	Modified Live Virus	Zoetis
[1]For Further Manufacture - These products represent one or more biologic fractions brought to a prescribed stage of production requiring further processing before becoming a completed or finished product.			

Figure 11. USDA-Licensed bovine coronaviral vaccines.

pathogenic agents can take years. Furthermore, a vaccine may not be available for a new infectious disease even after years of intensive research, as is the case with some diseases that have affected humans for many decades (for example, AIDS, dengue, and malaria). CoVs are notorious for responding poorly to therapeutics and vaccines, despite many years of research, and effective treatments or vaccines are not available for SARS-CoV, MERS, or any of the seasonal CoVs that affect humans. In domestic animals, most coronaviral vaccines provide only short, strain-specific protection against severe disease without sterile immunity, requiring multiple booster immunizations throughout the life of the animal. This feature allows coronaviruses to persist in animal populations and continue to be a significant threat to the farm animal industry. With the recent development of vaccines against SARS-CoV-2, we are learning that, as with veterinary coronaviral vaccines, the immunity provided by SARS-CoV-2 vaccines protects the infected person from developing severe disease but does not provide sterile immunity or stop viral shedding, with immunity appearing to be short-lived and requiring booster immunizations. Pandemics will continue to be a significant threat to human society. Preventing inter-species transmission by maintaining ecosystem boundaries at the animal/human interface is currently the best approach to avoiding future pandemics of zoonotic origin. We agree with others who recommend restricting or banning the trade of wild animals in live animal markets to reduce the risk of future coronavirus or other zoonotic pandemics.

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