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BIOLOGICAL ASPECTS OF THE INTERSPECIES TRANSMISSION OF SELECTED CORONAVIRUSES

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21.1 INTRODUCTION

Coronavirinae subfamily members are enveloped viruses with a helical capsid, and a positive-stranded nonsegmented RNA (27–32 kb) genome (Spaan et al., 1988; Tyrrell et al., 1975). The 5′ and 3′ends of coronavirus (CoV) genomes contain short untranslated regions (UTRs). For the coding regions, the genome organization of all CoVs is similar,

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with the characteristic gene order 5′-replicase ORF1ab, spike (S), envelope (E), membrane (M) and nucleocapsid (N)-3′, although variable numbers of additional ORFs are present in each subgroup of coronaviruses (Table 21.1). A transcription regulatory sequence (TRS) motif is present at the 3′ end of the leader sequence preceding most ORFs. Like other members of the *Nidovirales* order, CoVs produce a set of 3′ nested transcripts with a common short leader sequence at the 5′ terminus (Cavanagh, 1997; Gorbalenya et al., 2006; Spaan et al., 1988).

Coronavirus (CoV) genetic diversity is maintained through accumulation of point mutations in genes (genetic drift) due to low fidelity of the RNA-dependent RNA polymerase and homologous RNA recombination (genetic shift) (Domingo, 1998; Domingo et al., 1998a, b, 2006). Recombination is facilitated by a unique template switching "copy-choice" mechanism during RNA replication with the transcription-regulating sequence (TRS) motifs believed to direct it (Lai, 1992; Lai et al., 1985). Additionally, because CoVs possess the largest RNA genomes, their capacity for accommodating gene rearrangements and modifications (sometimes significant: such as in the porcine respiratory coronavirus (PRCV) spike gene deletion) is highest among all RNA viruses. This genetic plasticity allows CoVs to generate remarkable diversity in emergence of new strains and species and to adapt to new hosts and ecological niches without employing common biological vectors such as ticks, mosquitoes etc. Utilization of mechanical vehicles is not well documented, but is less likely to play a major role in CoV spread due to CoV instability in the environment (Sizun et al., 2000). An exception may be enhanced CoV stability when frozen permitting its increased transmission in winter.

Feline infectious peritonitis (FIP), first described in 1912 was presumably the earliest report of a CoV associated disease, whereas infectious bronchitis virus (IBV) was the first CoV isolated from chickens in 1937 (Beaudette and Hudson, 1937). This was followed by identification and characterization of murine hepatitis virus (MHV) and other mammalian CoVs in 1940s (Cheever and Daniels et al., 1949; Doyle and Hutchings, 1946).

Another two decades elapsed before CoV was recognized as the etiological agent of common colds in humans in 1965 (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1966). Later it was estimated that CoV infections contribute to as much as 35% of the total viral respiratory disease load during epidemics (Fielding, 2011). Overall, the proportion of adult colds caused by CoVs was estimated at 5% (McIntosh et al., 1970). Prior to the severe acute respiratory syndrome CoV (SARS-CoV) emergence and global pandemic in 2002–2003, it was commonly accepted that in humans CoVs cause mainly mild upper respiratory tract infections (Fielding, 2011), with the exception of human enteric CoV (HECV-4408) isolated from a child with acute diarrhea (Zhang et al., 1994). In contrast, in animals, CoVs cause a wide spectrum of clinical conditions including respiratory, enteric, hepatic and neurological diseases, with clinical outcomes ranging from mild symptomatology to lethal. The SARS epidemic has substantially advanced CoV research efforts, especially studies of CoV biodiversity and genomics. Since the discovery of SARS-CoV, numerous novel animal CoVs have been identified and characterized revealing a remarkable diversity of animal CoVs. The SARS-CoV was postulated to be of animal origin, with horseshoe bats as a potential natural reservoir (Lau et al., 2005; Li et al., 2005a). Besides SARS-CoV, bats are known to be reservoirs of important zoonotic viruses (including Ebola, Marburg, Nipah, Hendra, rabies and influenza) and viruses that can infect man or other animals (Calisher et al., 2006; Tong et al., 2012). Being abundant, diverse and geographically widespread, various species of bats, which are flying mammals equivalent to mosquitoes as insect vectors, were also recently shown to be natural hosts to a variety of CoVs (Calisher et al., 2006; Dominguez et al., 2007; Donaldson et al., 2010; Tang et al., 2006). Additionally,

TABLE 21.1. Coronavirus Genome Organization Comparison of Different Genera

Coronavirus	No. of nsp[a] in ORF1ab	No. of papain-like proteases in ORF1ab	No. of small ORFs between ORF1ab and N	No. of small ORFs downstream to N[b]	Conserved S[b] cleavage site presence	HE[b] gene presence
Alphacoronavirus						
Alphacoronavirus 1						
Transmissible gastroenteritis virus (TGEV)	16	2	2	1	N	N
Porcine respiratory coronavirus (PRCV)	16	2	1	1	N	N
Feline coronavirus (FCoV, FECV, FIPV)	16	2	4	2	N	N
Canine coronavirus (CCoV)	16	2	4	2	N	N
Human coronavirus NL63 (HCoV-NL63)	16	2	1	–	N	N
Human coronavirus 229E (HCoV-229E)	16	2	2	–	N	N
Porcine Epidemic diarrhea virus (PEDV)	16	2	1	–	N	N
Mink coronavirus (MCoV)	16	2	1	3	N	N
Ferret coronavirus (FeCoV)	16	2	1	2	N	N
Rhinolophus bat coronavirus HKU2 (BtCoV-HKU2)	16	2	1	1	N	N
Miniopterus bat coronavirus 1A/1B (BtCoV-1A/1B)	16	2	1	–	N	N
Betacoronavirus						
Subgroup A						
Human coronavirus HKU1 (HCoV-HKU1)	16	2	1	–	Y	Y
Human coronavirus OC43 (HCoV-OC43)	16	2	1	–	Y	Y
Canine respiratory CoV (CRCoV)	16	2	3	–	Y	Y
Mouse hepatitis virus (MHV)	16	2	2	–	Y	Y/N
Sialodacryoadenitis virus (SDAV)	16	2	2	1(?)	Y	Y
Bovine coronavirus (BCoV)	16	2	3	–	Y	Y
Porcine hemagglutinating encephalomyelitis virus (PHEV)	16	2	2	–	Y	Y
Equine coronavirus (ECoV)	16	2	2	–	Y	Y

(*Continued*)

TABLE 21.1. (*Continued*)

Coronavirus	No. of nsp[a] in ORF1ab	No. of papain-like proteases in ORF1ab	No. of small ORFs between ORF1ab and N	No. of small ORFs downstream to N[b]	Conserved S[b] cleavage site presence	HE[b] gene presence
Human enteric coronavirus 4408 (HECV-4408)	16	2	3	–	Y	Y
Subgroup B						
Severe acute respiratory syndrome coronavirus (SARS-CoV)	16	1	7	–	N	N
SARS-related Rhinolphus bat coronavirus HKU3 (Bat SARS-CoV)	16	1	5	–	N	N
Subgroup C						
Tylonycteris bat coronavirus HKU4 (BtCoV-HKU4)	16	1	4	–	N	N
Pipistrellus bat coronavirus HKU5 (BtCoV-HKU5)	16	1	4	–	N	N
Subgroup D						
Rousettus bat coronavirus HKU9 (BtCoV-HKU9)	16	1	1	2	N	N
Gammacoronavirus						
Infectious bronchitis virus (IBV)	15	1	4	–	Y	N
Turkey coronavirus (TCoV)	15	1	5	–	Y	N
Beluga whale coronavirus	15	1	8	–	N	N
Deltacoronavirus						
Bulbul coronavirus HKU11	15	1	1	3	N	N
Thrush coronavirus HKU11	15	1	1	3	N	N
Munia coronavirus HKU11	15	1	1	3	N	N

[a]*nsp, non-structural protein*
[b]*N, nucleoprotein; S, spike protein; HE, haemagglutinin esterase*

a novel highly divergent CoV was reported recently in a captive deceased beluga whale (Mihindukulasuriya et al., 2008) emphasizing once more the great adaptability and widespread prevalence of *Coronavirinae* subfamily members.

In this chapter, we first summarize recent studies by us and others on coronavirus biodiversity and genomics. Secondly we discuss the biologic factors that contribute to novel CoV emergence and interspecies jumping with emphasis on animal CoVs.

21.2 CORONAVIRUS CLASSIFICATION AND PATHOGENESIS

Coronaviruses (CoVs) belong to the order *Nidovirales*, family *Coronaviridae*. Classification into three (1 to 3) antigenic groups was initially established based on antigenic cross-reactivity, and was further confirmed by phylogenetic analysis (Lai and Holmes, 2001). Historically, within each group, subgroups (provisional subgroups) were sequentially established: in group 1—1a and 1b were defined; in group 2—2a, 2b, 2c and 2d; and in group 3—3a, 3b and 3c; however, some of these taxonomic units were contentious. The abundance and complexity of new data on novel CoV phylogeny post-SARS epidemic, and especially the availability of complete genomic sequences, revealed a need to revise the existing CoV taxonomy. Therefore, within the *Coronaviridae* family, two subfamilies were recently defined: *Coronavirinae* and *Torovirinae* (International Committee on Taxonomy of Viruses (ICTV; 2009). The *Coronavirinae* subfamily is further subdivided into three genera: *alphacoronavirus* (formerly CoVs group 1), *betacoronavirus* (formerly group 2) and *gammacoronavirus* (formerly group 3), with *alphacoronavirus 1 species* corresponding to former subgroup 1a (transmissible gastroenteritis virus (TGEV), PRCV, canine coronavirus (CCoV) and feline coronavirus (FCoV)) and other alphacoronavirus species (formerly subgroup 1b) each represented by different CoVs (human coronavirus NL63 (HCoV-NL63), human coronavirus 229E (HCoV-229E), porcine epidemic diarrhea virus (PEDV) etc.) from various hosts (Gonzalez et al., 2003) (Figure 21.1). No new species (or other relevant taxonomic units) were established to replace the former subgroups 2a–2d. Therefore, the majority of prototype mammalian and human CoVs are currently distributed between the *alpha-* and *betacoronavirus* (subgroup 2a) genera; while the *betacoronavirus* subgroup 2b is represented by the SARS- and SARS-like CoV species and *betacoronavirus* subgroups 2c and 2d include bat CoV (BtCoV) species. Gammacoronaviruses are detected primarily in domestic birds or related avian species. Gough and colleagues have recently identified a parrot CoV that is genetically distinct from alpha-, beta-, and gammacoronaviruses (Gough et al., 2006). Additional novel CoVs that are genetically similar to the parrot coronavirus were subsequently detected in terrestrial birds (Woo et al., 2009). Therefore, CoVs of this novel lineage recently have been proposed to form a new genus, provisionally named *deltacoronavirus* (de Groot et al., 2011) that included some species from the former provisional subgroup 3c. Additionally, findings from other studies suggested that there is much diversity in CoVs circulating in wild birds (Hughes et al., 2009; Muradrasoli et al., 2010). Recently conducted phylogenetic analyses of diverse avian CoVs demonstrated that there are various gammacoronaviruses and deltacoronaviruses circulating in birds. Gammacoronaviruses were found predominantly in *Anseriformes* birds, whereas deltacoronaviruses could be detected in *Ciconiiformes*, *Pelecaniformes*, and *Anseriformes* birds (Chu et al., 2011). Chu et al. (2011) also suggested that there is frequent interspecies transmission of gammacoronaviruses between duck species; whereas deltacoronaviruses may have more stringent host specificities (Chu et al., 2011). Furthermore, a novel virus from a beluga whale that died of generalized pulmonary disease and terminal acute liver failure was suggested to be a highly divergent *Coronavirinae* member most closely related to *gammacoronavirus* genus members (former subgroup 3b) (Mihindukulasuriya et al., 2008). If so, this finding could be the first evidence of mammalian non-alpha-, non-betacoronaviruses. It also suggests the possibility of intriguing CoV circulation between birds and aquatic mammals.

Genomic organization within each CoV genus has some unique features and provides data that support most of the newly established taxonomic units (Table 21.1). However, the

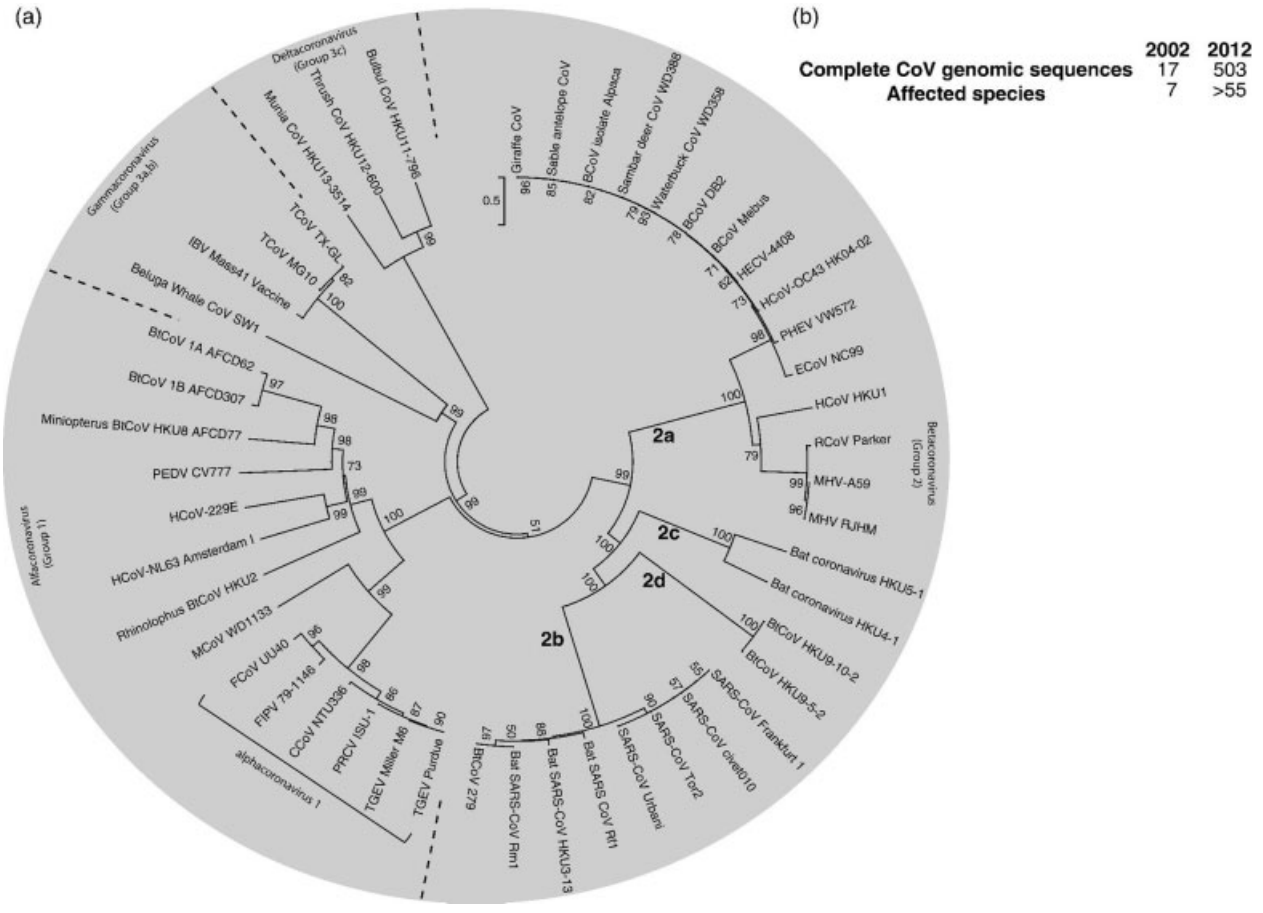

Figure 21.1. (**a**) Neighbour-joining phylogenetic tree based on the complete genome sequences of representative alpha-, beta-, gamma- and deltacoronaviruses. The genera are named as described in the 9th report of the International Committee on Taxonomy of Viruses with the former group names in brackets. Additionally, *alphacoronavirus 1* species and subgroups 2a-2d are indicated. Bootstrap support values are indicated. Scale bar indicates number of nucleotide substitutions per site. ClustalW algorithm was used to generate the tree in MEGA 5.05 software. (**b**) The summary indicates the approximate numbers of the complete genomic sequences released and species affected by those CoVs prior (2002) to after (2012) the SARS outbreak.

rapidly accumulating novel and vast CoV genomic data may result in further revisions of the *Coronaviridae* nomenclature.

Coronavirus infection can be asymptomatic or can cause respiratory, intestinal, hepatic and neurological disease with a wide range of clinical manifestations. The molecular mechanisms of the pathogenesis of several CoVs have been actively studied since the 1970s (Weiss and Navas-Martin, 2005). Some CoVs of animal origin, such as TGEV, bovine CoV (BCoV), and avian IBV, are of veterinary importance. Other animal CoVs warrant careful monitoring because they infect domestic animals (pets) living in close proximity to humans (such as CCoV and feline infectious peritonitis virus (FIPV)) or may serve as natural reservoirs for emerging CoVs persisting in wild animals (bats, wild ruminants or wild carnivores). Feline CoV which causes inapparent-to-mild enteritis in cats and sometimes leads to fatal effusive abdominal FIP is a pathogenesis paradigm for the scientific community (Pedersen et al., 2008). Additionally, preexisting immunity was shown to accelerate and exacerbate the severity of this disease (Pedersen et al., 1984b). A range of MHV strains are recognized with different tissue tropisms and levels of virulence (Navas-Martin et al., 2005). The MHV and PRCV are studied as models for human disease. The MHV infection of the mouse is regarded as one of the best animal models for the study of demyelinating diseases such as multiple sclerosis (Weiss and Navas-Martin, 2005). Because the pulmonary pathology of PRCV in pigs resembles that of SARS patients, the effect of dexamethasone treatment and a pre-existing respiratory viral infection on PRCV pathogenesis and immune responses was studied in detail as a model for SARS-CoV (Jung et al., 2007, 2009; Zhang et al., 2008). The SARS-CoV pathogenesis is unique among HCoVs which normally cause only mild upper respiratory tract disease (Ding et al., 2004; Drosten et al., 2003a, b; Ksiazek et al., 2003; Sims et al., 2008). The SARS-CoV which causes acute respiratory distress, especially in the elderly, provides a demonstration of how CoVs acquired via recent interspecies transmission events can cause excessive and sometimes dysregulated innate immune responses in new hosts (Perlman and Dandekar, 2005; Smits et al., 2010; Yoshikawa et al., 2009). Undoubtedly, the variety of clinical diseases in animals and the mainly respiratory pathology in humans caused by CoVs requires further detailed studies of CoV pathogenesis. The accumulated data indicate that CoV tissue tropism and virulence are not defined solely by the cellular receptor exploited or the genetic relatedness among strains, but rather result from the interplay of individual viral gene products and the host immune responses (Table 21.2) (de Groot et al., 2011). There are numerous reports indicating that S, N and some accessory non-structural proteins (nsps) may govern or affect CoV tissue tropism and virulence (Cowley and Weiss, 2010; Cowley et al., 2010; Frieman et al., 2012; Herrewegh et al., 1995; Rottier et al., 2005; Sanchez et al., 1999; Yeager et al., 1992). It is also believed that pathogenesis is determined by viral quasispecies rather than by the action of a single genotype (Vignuzzi et al., 2006). Another significant feature of CoV pathogenesis, possibly related to the existence of quasispecies, is the often dual pneumoenteric tropism, even in case of one dominating syndrome (Leung et al., 2003; Park et al. 2007; Shi et al., 2005; Zhang et al., 2007).

21.3 NATURAL RESERVOIRS AND EMERGENCE OF NEW CORONAVIRUSES

An estimated 75% of emerging diseases arise from zoonotic sources (Taylor et al., 2001). There are two essential conditions for emergence of novel viruses and sustainability in a new host: within-natural host population growth and between-host transmission efficiency

TABLE 21.2. Major Coronavirus Associated Diseases and Pathotypes In Different Hosts.

Pathotype	Coronavirus	Cellular receptor (Chu et al., 2006; Madu et al. 2007; Oh et al., 2003; Weiss and Navas-Martin, 2005)	Genus	Disease/syndrome	Host/age	Severity
Respiratory	HCoV-NL63	ACE2	*Alphacoronavirus*	Common cold, croup	Human/any	Mild
	HCoV-229E	Human APN	*Alphacoronavirus*	Common cold, upper respiratory tract disease	Human/any	Mild
	PRCV	Porcine APN	Alphacoronavirus	Respiratory disease	Pig/any	Mild
	HCoV-HKU1	Neu5,9Ac2-containing moiety	Betacoronavirus	Common cold, upper respiratory tract disease	Human/any	Mild
	HCoV-OC43	Neu5,9Ac2-containing moiety	*Betacoronavirus*	Common cold, upper respiratory tract disease	Human/any	Mild
	CRCoV	ND	*Betacoronavirus*	Respiratory disease	Dog/any	Mild
	SDAV	ND	*Betacoronavirus*	Respiratory disease	Rats/any	Mild
	BRCV[a]	Neu5,9Ac2-containing moiety	*Betacoronavirus*	Respiratory disease, anorexia, shipping fever	Cow/any	Mild
	SARS-CoV	ACE2	*Betacoronavirus*	Acute Respiratory distress, pneumonia	Human/adults and elderly	Mild-severe (may be lethal in immuno-compromised and elderly)
	IBV	α2,3-linked sialic acid + heparan sulfate	*Gammacoronavirus*	Respiratory disease, reproductive disorder	Chicken/any	Mild-severe
Enteric	TGEV	Porcine APN	*Alphacoronavirus*	Enteritis	Pig/any, more severe in young (<2–3 weeks)	Moderate-severe (may be lethal in young piglets)
	PEDV	Porcine APN	*Alphacoronavirus*	Enteritis	Pig/any	Moderate-severe (may be lethal in young piglets)
	FCoV	Feline APN	*Alphacoronavirus*	Enteritis	Cat/any	Asymptomatic-Mild
	CCoV	Canine APN	*Alphacoronavirus*	Enteritis	Dog/puppies	Mild-severe-lethal

	BECV[b]	Neu5,9Ac2-containing moiety	*Betacoronavirus*	Winter dysentery Enteritis	Cow/any	Moderate-severe
	ECoV	ND	*Betacoronavirus*	Enteritis, fever	Horse/any	Moderate
	PHEV	Neu5,9Ac2-containing moiety	*Betacoronavirus*	Vomiting and wasting disease[c]	Pig/<1 month	Severe-deadly
	HECV-4408	ND	*Betacoronavirus*	Acute diarrhea	Human/children	Moderate (Zhang et al., 1994)
	SARS-CoV	ACE2	*Betacoronavirus*	Diarrhea[d]	Human/adults and elderly	Moderate
	TCoV	ND	*Gammacoronavirus*	Enteritis	Turkey/poults	Moderate-severe
Hepatic	MHV	Murine CEACAM1	*Betacoronavirus*	Hepatatis	Mouse/any	Severe-lethal
Neurological	MHV	Murine CEACAM1	*Betacoronavirus*	Encephalitis, CNS demyelination	Mouse/any	Severe-lethal
	PHEV	Neu5,9Ac2-containing moiety	*Betacoronavirus*	Hemagglutinating encephalomyelitis	Pig/<1 month	Severe-lethal
Reproductive	IBV	α2,3-linked sialic acid + heparan sulfate	*Gammacoronavirus*	Reproductive disorder (egg production drop)	Chicken/adults	Mild
	TCoV	ND	*Gammacoronavirus*	Reproductive disorder (egg production drop), poor growth	Turkey/adults	Mild
Systemic	FIPV	Feline APN	*Alphacoronavirus*	Infectious peritonitis with systemic granulomatous-necrotizing lesions	Cat/any	Severe-lethal
Other	SDAV	ND	*Betacoronavirus*	Conjuctivitis	Rats/any	Asymptomatic-mild
	BtCoV	ND	*Alphacoronavirus* *Betacoronavirus*	Asymptomatic	Bat(various species)/any	Asymptomatic-mild

[a] *BRCV, Bovine respiratory CoV*

[b] *BECV, Bovine enteric CoV*

[c] *Suggested to be induced by vagus nerve damage, therefore may be not a true enteropathogenic effect*

[d] *Although reported, diarrhea was not a major symptom in SARS patients, but with the exceptions noted in Hong Kong (Amoy Gardens) and among medical care workers at Chang Gung Memorial Hospital, Kaohsiung Medical Center (Chiu et al., 2004; Peiris et al., 2003a).*

(Dennehy et al., 2006). Viral fitness is critical in source (reservoir, original) and sink (new) hosts and may be poor initially in a new host with subsequent genetic adaptation to establish a persistent population and/or epidemiological spread as in the case of SARS-CoV (Dennehy et al., 2006; Li et al., 2005b; Qu et al. 2005).

The natural reservoirs of CoVs and their precise emergence pathways remain largely unknown. For some CoVs, persistently or chronically infected (asymptomatic) animals, birds and humans may serve as a source of infection and in favorable conditions may lead to disease outbreaks (An et al., 2011; Che et al., 2006; Dominguez et al., 2007; King et al., 2011; Lee et al., 2003; Tang et al., 2006; Vogel et al., 2010; Walsh et al., 1999; Watanabe et al., 2010; Wilder-Smith et al., 2005) http://www.savsnet.co.uk/canine-enteric-coronavirus/. Increasing evidence indicates that CoV quasispecies lead to the selection of new viral forms and to the sporadic emergence of new viral species with virulent phenotypes (Domingo, 1998; Domingo et al., 1998a, b, 2006; Holland et al., 1982). For some CoVs, there is evidence that they have emerged as a result of recombination between existing CoVs. For instance FIPV, is closely related to TGEV and CCoV and may have initially emerged as a result of recombination between CCoV and FCoV type I (Herrewegh et al., 1998). The hypothesis that FIPV is a relatively common natural mutant of FCoV—the within-host spontaneous mutation theory—was suggested by Vennema et al (Vennema et al., 1998). The PRCV is another example of a new CoV emergence due to a natural mutation in TGEV within the swine host (Laude et al. 1993; Pensaert et al., 1986; Wesley et al., 1990). Other CoVs (HECV-4408, HCoV-OC43, SARS-CoV, etc.), may have evolved as a result of inter-species transmission events and adaptation to new hosts due to close cohabitation, translocation or handling/consumption of infected animal by-products (Guan et al., 2003; Lau et al., 2005; Li et al., 2005a; Vijgen et al., 2005; Zhang et al., 1994).

Since the emergence of SARS, knowledge of CoV molecular epidemiology and genomics has increased greatly. However, identification of the CoV common ancestors or source remains a challenging task requiring a comprehensive understanding of CoV ecology and the factors affecting it. It is noteworthy that according to the current *Coronavirinae* subfamily classification, all known mammalian CoVs belong to *alpha-* and *betacoronavirus* genera, while *gamma-* and newly emerging *deltacoronavirus* genera comprise exclusively (or predominantly) avian CoVs (Woo et al., 2010, 2012). Furthermore, while CoVs from bat species, omnivores and carnivores are uniformly distributed between *alpha-* and *betacoronavirus* genera, CoVs from herbivores appear to be strictly confined at present to the *betacoronavirus* genus. These observations indicate that the type of feeding and digestive system may affect the ecology and evolution of CoVs along with host species mobility and prevalence. Bats constitute 20% of the mammalian population on Earth being the most divergent and widely distributed nonhuman mammalian species (Dominguez et al., 2007). Numerous recent studies indicate that bats harbor a much wider diversity of CoVs than any other mammalian/avian species (Donaldson et al., 2010; Vijaykrishna et al., 2007). Molecular clock analysis indicates that BtCoVs are evolutionarily older than CoVs from any other animals, with analysis of population dynamics indicating that CoVs in bats have constant population growth and that viruses from all other hosts show epidemic-like increases in population (Vijaykrishna et al., 2007). This indicates that diverse CoVs are endemic in different bat species, and that they may account for repetitive CoV introductions into and occasionally permanent establishment in other species (Vijaykrishna et al., 2007). It is also interesting that BtCoVs are found in both *alpha-* and *betacoronavirus* genera, but not yet in *gammacoronavirus* genus, suggesting that BtCoVs may be ancestral to all mammalian CoVs but not to CoVs from avian species (Figure 21.2). A recent report documented mammalian CoVs in the *deltacoronavirus* genus and suggested an avian

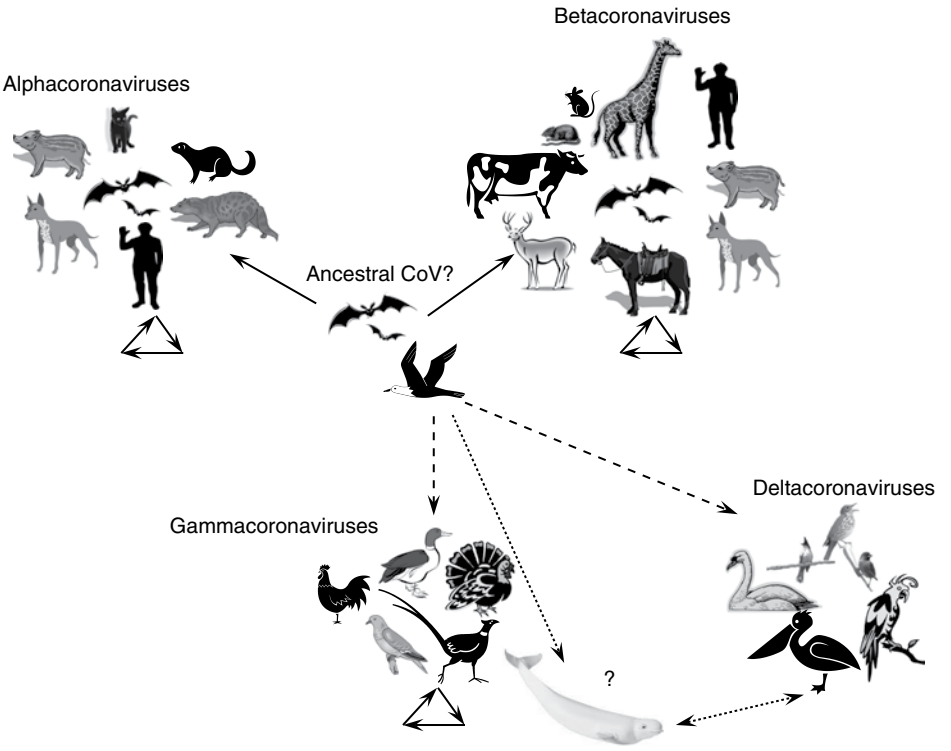

Figure 21.2. Tentative schematic of CoV ecology in diverse hosts. Solid and dashed lines represent confirmed and hypothetical interspecies transmission pathways, respectively; and arrow triangles indicate confirmed interspecies transmission within each genera; "?" means suggested but not confirmed.

ancesteral CoV as the source of genes for *gamma-* and *deltacoronavirus* (Woo et al., 2012) (Figure 21.2). Alternatively, avian CoVs could have split off earlier from the ancestral CoV and diverged significantly over time evolving separately from mammalian CoVs.

Recent studies of BtCoVs in China demonstrated that genetically divergent CoVs are present in and are species-specific in different bats (Tang et al., 2006). Moreover, the same group demonstrated that there is an additional isolated sublineage of CoVs (possibly non-*alpha-*, *beta-* or *gammacoronavirus*) consisting of exclusively BtCoVs, further emphasizing their extraordinary genetic diversity that affects the entire CoV taxonomy (Tang et al., 2006). Overall, BtCoV abundance, absence of epidemic patterns with only asymptomatic cases identified to date and the remarkable viral-host fitness indicate that bats can play a central role in CoV ecology and persistence (Dominguez et al., 2007; Vijaykrishna et al., 2007). Therefore, bat species and other animals sharing ecological niches with bats should be carefully monitored for CoV persistence, diversity and interspecies adaptation.

Highly diverse avian CoVs, also suggested to form new and separate (from mammalian CoVs) genera, do not seem to account for new CoV emergence and the current alpha- and betacoronavirus diversity in mammalian species including humans (Chu et al., 2011; Gough et al., 2006; Hughes et al., 2009; Muradrasoli et al., 2010; Woo et al., 2012). However, they may affect the entire CoV evolution and ecology through unknown pathways and, therefore, should also be under surveillance (Woo et al., 2012).

21.4 ALPHA-, BETA- AND GAMMA CORONAVIRUSES: CROSS-SPECIES TRANSMISSION

Frequent host-shifting events are characteristic for CoV evolution and phylogeny. They are represented by frequent animal-to-animal and occasionally animal-to-human (zoonosis) interspecies transmission events (Lau et al., 2005; Graham and Baric, 2010; Guan et al., 2003; Rota et al., 2003). A suspected case of SARS-CoV human-to-animal (reverse zoonosis) transmission was reported (Chen et al., 2005). Furthermore, CoV interspecies transmission and subsequent establishment in a new host may be facilitated through direct spread (original host → new host) as was observed for bovine and wild ruminant CoVs (Alekseev et al. 2008; Hasoksuz et al., 2007; Tsunemitsu et al., 1995) or involving an intermediate host (original host → intermediate host → new host) in the case of SARS-CoV (Peiris et al., 2003a, b, 2004; Zhong et al. 2006).

There are multiple examples of CoV interspecies transmission within each *alpha-*, *beta-* and *gammacoronavirus* genera (Alekseev et al., 2008; Hasoksuz et al., 2007; Jin et al., 2007; Lorusso et al., 2008, 2009; Peiris et al., 2003b, 2004; Perlman and Netland, 2009; Pfefferle et al., 2009; Tsunemitsu et al., 1995; Vijgen et al., 2006; Zhong et al., 2006) (Figure 21.2). Under experimental conditions turkey poults were shown to be susceptible to BCoV infection (Ismail et al., 2001), and close antigenic relationship between turkey and bovine CoVs was suggested based on cross-seroneutralization and hemagglutination-inhibition assay results (Dea et al., 1990). However, there are no reports of natural interspecies CoV adaptation or recombination events between CoVs from different genera.

Significant gene modifications (often deletions in accessory nsps or spike protein genes) or rearrangements (deletion or insertion of the whole ORFs encoding accessory nsps) are often involved in or follow host-shift or tissue tropism change events (Hasoksuz et al., 2007; Laude et al., 1993; Lorusso et al., 2008; Vaughn et al., 1995; Vennema et al., 1998; Vijgen et al., 2005); while scattered genome-wide point mutations normally reflect within host evolution of CoVs (Zhang et al., 2006, 2007) (Table 21.3).

21.4.1 Alpha-coronaviruses cross-species transmission

The pleiotropic molecular mechanisms that govern cross-species transmission of alphacoronaviruses are not completely understood but homologous recombination following co-infection with different CoVs appears to be a common route of generation of new sustainable CoV populations in heterologous hosts (Decaro et al., 2008a, 2010; Lorusso et al., 2008). Recombinants between TGEV, CCoV and FCoV, that represent host range variants of the same CoV species, are known to occur (Benetka et al., 2006; Decaro et al., 2009, 2010; Herrewegh et al., 1998; Pedersen et al., 1981; Wesley, 1999). Canine CoVs illustrate the genetic evolution and complexity of alphacoronaviruses. There are two CCoV genotypes identified to date, CCoV-I and CCoV-II (Decaro et al., 2008a). Based on the high genetic relatedness between the CCoV-II and TGEV genomes and on the presence of ORF3 remnants in both genomes, it has been hypothesized earlier that TGEV originated from CCoV-II through cross-species transmission (Lorusso et al., 2008). More recently, novel CCoV-II strains have been isolated, which likely originated from a double recombination event with TGEV, occurring in the 5′ end of the spike protein gene (Decaro et al., 2009; Erles and Brownlie, 2009).

While FCoV replication is primarily restricted to the mature intestinal epithelial cells (Pedersen et al., 1981, 1984a), virulent FIPV strains exhibit a prominent tropism for macrophages (Pedersen, 1976; Petersen and Boyle, 1980) with a rapid dissemination of the

TABLE 21.3. Coronaviruses that Emerged as a Result of Interspecies Transmission or Tissue Tropism Changes and Suggested Associated Genomic Modifications

Resulting CoV/host	Suspected original CoV/host	Genomic modification	References
TGEV/pig	CCoV-II/dog	ORF3 insertion	Decaro et al. (2007)
CCoV-II/dog	TGEV/pig	Recombination in the 5′ end of the spike gene	Decaro et al. (2009)
CCoV-II/dog	CCoV-I/dog and unknown CoV	Recombinant spike gene	Lorusso et al. (unpublished)
FIPV/cat	FCoV/cat and CCoV/dog	Substitutions in M and ORF7b genes and FCoV-CCV recombinations in spike and pol genes	Brown et al., (2009), Herrewegh et al. (1998)
PRCV/pig	TGEV/pig	621–681-nt deletion in the 5′ end of the spike gene; deletions in ORF3	Wesley et al. (1991)
HCoV-OC43/human	BCoV/cow	290-nt deletion (corresponding to the absence of BCoV nsp 4.9 kDa and nsp 4.8 kDa)	Vijgen et al. (2005)
HECV-4408/human	BCoV/cow	?	
GiCoV/giraffe	BCoV/cow	Deletion in the S1 subunit (amino acid 543–547) of the spike protein	Hasoksuz et al. (2007)
SARS-CoV/human	Bat and civet SARS-CoV/ horseshoe bat and civet cats	29-nt deletion in ORF8 and substitutions in spike gene and ORF3	Lau et al. (2005)

? means not known.

virus throughout the body. Feline coronavirus (FCoV or FIPV) naturally infects domestic and wild *Felidae*. People are not susceptible, but dogs and swine can be experimentally infected with FIPV (Pedersen, 2009). A mild to moderately severe TGE-like syndrome occurs in baby pigs post FIPV infection (Woods et al., 1981). It is noteworthy that FIP appeared within a decade of the initial descriptions of TGE in pigs in North America in 1946 (Doyle and Hutchings, 1946; Haelterman, 1962; Haelterman and Hutchings, 1956; Pedersen, 2009). At least one strain of CCoV can induce mild enteritis in cats and enhance a subsequent infection with FIPV, indicating a special closeness to FCoVs (McArdle et al., 1992). Therefore, empirical data indicate that CCoV may be a parent of FCoV in this scenario (Pedersen et al., 2008, 2009).

21.4.2 Beta-coronaviruses cross-species transmission

Among betacoronaviruses, interspecies transmission events appear to be very common even between genetically distant hosts. There are at least two human CoVs of suspected bovine origin—HCoV-OC43 and HECV-4408 (Vijgen et al., 2005; Zhang et al., 1994). Bovine CoVs and HCoV-OC43 show remarkable genetic and antigenic similarities and utilize the same cellular receptor (Table 21.2). Interestingly, while HCoV-OC43 is fairly common in humans, causing mild respiratory disease (Huang et al., 2009), human enteric CoV 4408 which also shares high genetic and antigenic similarity with BCoV (Han et al., 2006), appears to be an isolated case scenario (Zhang et al., 1994). This may indicate that fecal-oral transmission and therefore enteric pathology is not very common

among HCoVs or that HCoV-OC43 was introduced into the human population earlier in the past (Vijgen et al., 2005) and now possesses better host fitness properties than HECV-4408. There are also multiple examples of BCoV (or its host range variants) interspecies transmission between related species of ruminants including white tail deer, waterbuck, sable antelope, giraffe, and water buffalo (Decaro et al., 2008c; Hasoksuz et al., 2007; Tsunemitsu et al., 1995).

Persistent MHV infection *in vitro* resulted in the emergence of host range variants capable of efficient replication in normally nonpermissive cell lines derived from non-mouse hosts including Chinese hamster ovary (CHO), human hepatocellular liver carcinoma (HepG2), and in human breast adenocarcinoma (MCF7) (Baric et al., 1999). In another study, host range MHV mutants were isolated from mixed cultures containing progressively increasing concentrations of nonpermissive Syrian baby hamster kidney (BHK) cells and decreasing concentrations of permissive murine astrocytoma (DBT) cells (Hensley et al., 1998).

Emergence of SARS-CoV is the most recent, most significant and best documented event of betacoronavirus interspecies transmission (Drosten et al., 2003b; Ksiazek et al., 2003; Peiris et al., 2004). Although the discovery of SARS-CoV in palm civets and raccoon dogs from live animal markets in China had initially identified them as an immediate source of the SARS-CoV infection in humans, subsequent surveillance in wild areas suggested that they may have only served as an amplification host for SARS-CoV (Lau et al., 2005). Genomic analyses, efficiency of civet ACE2 receptor binding to SARS-CoV S proteins from different stages of the SARS epidemic (Li et al., 2005b) and lack of widespread SARS-CoV infection among farmed civets (Tu et al., 2004) revealed that they were likely not a natural reservoir of human SARS-CoV (Table 21.3). The prevalence of SARS-like CoVs (~40%) and SARS-CoV specific antibodies (>60%) among Chinese horseshoe bats in Hong Kong, together with the high genetic similarities between the bat and human SARS-CoVs provided evidence for bats as a potential natural host of SARS-CoV infection in humans (Lau et al., 2005). Later epidemiological investigations suggested categorizing SARS outbreaks into three groups: interspecies, early-mid epidemic in humans and late epidemic, with each one revealing successive steps of SARS-CoV adaptive evolution in humans. Twelve amino acid sites in the S protein (with a larger proportion (24%) of them located in the receptor-binding domain) were identified as being under positive selective pressure and potentially responsible for SARS-CoV adaptation to new hosts (Zhang et al., 2006). Therefore, SARS-CoV emergence followed a common pattern for zoonoses: natural reservoir (bats) → intermediate host (civets) → new host (humans) → adaptation (viral-host fitness optimization) within the new host (humans).

It is interesting that cats, ferrets, several inbred mouse species (BALB/c, C57BL/6 (B6), 129S) and palm civets were all susceptible to natural or experimental infection with SARS-CoV Urbani strain (Glass et al., 2004; Hogan et al., 2004; Martina et al., 2003; Roberts et al., 2005; Subbarao et al., 2004; Wu et al., 2005). Additionally, a mink lung cell line (Mv1Lu) was permissive to SARS-CoV, expressing a functional ACE2 receptor for viral entry (Gillim-Ross et al., 2004; Heller et al., 2006; Mossel et al., 2005). This represents a wide range of susceptible species which may be a result of the relatively recent interspecies transmission event, ongoing adaptation and incomplete host fitness. The HCoV-OC43 according to molecular clock dating was transmitted from the bovine species to humans around 1890 (Vijgen et al., 2005). These betacoronaviruses share high genetic similarities and possibly a common ancestor with canine respiratory CoV (CRCoV) and PHEV, all of which appear to be species-specific CoVs due to a prolonged evolution and host fitness optimization (Vijgen et al., 2006).

21.4.3 Gamma-coronaviruses cross-species transmission

There is no indisputable evidence for interspecies transmission of known avian CoVs to phylogenetically distant hosts. Frequent interspecies transmissions of gammacoronaviruses between duck species were recently reported by Chu et al. (2011). However, in this case it is hard to establish the boundary between true interspecies transmission and host range CoV variants circulating among related host species. This scenario is similar to the close genetic relatedness among betacoronaviruses circulating among various ruminant species (Alekseev et al. 2008; Hasoksuz et al., 2007; Tsunemitsu et al., 1995). Isolation of avian IBV from domestic peafowl (*Pavo cristatus*) and teal (*Anas*) in China (Liu et al., 2005) reveals a potential for interspecies transmission of gammacoronaviruses or may be indicative of a wider natural host range. The latter is supported by the fact that TCoV strains have been successfully propagated in embryonated chicken and turkey eggs by inoculation of the amniotic cavity (Nagaraja and Pomeroy, 1997).

A suspected interspecies transmission event in the case of a captive beluga whale CoV, provisionally classified as a gammacoronavirus (Mihindukulasuriya et al., 2008), is supported by genetic data and sharing of ecological niches between aquatic mammalian and aquatic avian species. Whether the captive beluga whale initially acquired a CoV from a cohabitating avian species or if they share a common CoV ancestor is unclear (Mihindukulasuriya et al., 2008). However, the widespread presence of gammacoronaviruses in aquatic avian species (Chu et al., 2011) and the clinical severity (generalized pulmonary disease and acute liver failure) of the CoV infection in the beluga whale (Mihindukulasuriya et al., 2008) may be indicative of bird-to-whale CoV transmission. Sharing of a common ancestral CoV between avian species and the deceased beluga whale remains a possibility. Disease severity and death can be attributed to a number of factors including within host spontaneous CoV mutation resulting in higher virulence or immune incompetence.

The provisional *deltacoronavirus* genus includes parrot, thrush, bulbul and other terrestrial bird CoVs (Chu et al., 2011; Gough et al., 2006; Woo et al., 2009). Deltacoronaviruses infect and co-circulate with gammacoronaviruses in a variety of *Galloanserae*, *Neoaves* and *Passeriformes* (Chu et al., 2011). Although Chu and colleagues (Chu et al., 2011) suggested that deltacoronaviruses may have more stringent host specificities, reports by Woo et al. (Woo et al., 2009, 2012) indicate possible interspecies transmission of deltacoronaviruses from birds to an Asian leopard and pig.

21.5 ANTHROPOGENIC FACTORS AND CLIMATE INFLUENCE ON CORONAVIRUS DIVERSITY AND OUTBREAKS

With the world's population exceeding seven billion and the ability to travel long distances within a short timeframe, humans are one of the most significant modifying influences on viral ecology, including that of CoVs. Besides the contributions of population density and mobility of humans, to CoV emergence and spread as exemplified by the SARS-CoV epidemic, there are numerous sociodemographic influences that can affect CoV ecology and evolution. These include: global disease control efforts, improvements in public health infrastructure (public health training, emergency response, and prevention and control programs), improvement in veterinary care, alterations of natural animal habitats and land-use influences (deforestation, agricultural development, water projects, and urbanization) and shifting ecological niches (farming and exotic animal farming, animal transportation,

selection and breeding, preservation of endangered species in captivity, introduction of feral animals back into wild habitats, etc.) (Patz et al., 2003).

There was a dramatic shift in the status, keeping, and breeding of cats and dogs as pets in the second half of the twentieth century. The numbers of pet cats/dogs greatly increased, purebreeding and cattery/kennel rearing became increasingly popular, and more cats and dogs were placed in shelters. These large multiple cat/dog indoor environments are known to favor feline and canine enteric CoV infections and FIP (Pedersen, 2009). The increasing demand for farm animals (such as pigs, cows, horses) that are often kept in close proximity to cats and dogs or exposed to wild rodents, bats or carnivores creates favorable conditions for genetic exchange between different species of CoVs. This can result in continuous emergence of new (recombinant) or mutant CoVs, thereby increasing their diversity as previously described for TGEV and CCoV (Decaro et al., 2009; Lorusso et al., 2008). Captive exotic wild ruminants (giraffe, waterbuck and Sable antelope) from Africa were transported and kept in captivity in the US in wildlife parks where they may have acquired BCoV from domestic ruminants resulting in similar diarrheal disease outbreaks (Alekseev et al. 2008; Hasoksuz et al., 2007; Tsunemitsu et al., 1995). It is unknown, whether two human CoVs—HCoV-OC43 and HECV-4408—derived from BCoV (Vijgen et al., 2005; Zhang et al., 1994) were acquired through handling/consumption of dairy or beef products or through a direct contact with infected cattle.

Identification and characterization of novel CoVs in farmed mink and ferrets in the US (Gorham et al., 1990; Vlasova et al., 2011; Wise et al., 2006, 2010) reveals a need for extensive wildlife surveillance to rule out anthropogenic influences in emergence of these pathogens. The SARS-CoV emergence and pandemic provide a vivid illustration of how modern anthropogenic activities can facilitate CoV introduction and spread in humans. On the other hand, the timely applied strict control and intervention measures curtailed the infection (Drosten et al., 2003a; Ksiazek et al., 2003; Peiris et al., 2003b). Crowded housing of the exotic civet cats intended for human consumption in animal markets in China and within restaurants fostered the spread of SARS-like CoV in this intermediate host and its initial spill-over into the human population. International travel facilitated the spread of this "atypical pneumonia" worldwide (Drosten et al., 2003b; Ksiazek et al., 2003; Lau et al., 2005; Peiris et al., 2003b). After the danger was recognized, the prompt search for the etiological agent, its discovery and detailed scientific characterization, together with a WHO issued travel advisory and extensive medical treatment of affected patients, may have restrained the wider expansion of this new virus before its adaptation to the human host was complete (Guan et al., 2004; Lau et al., 2005; Li et al., 2005a; Peiris et al., 2003a). Interestingly, although civet cats from Chinese animal markets were commonly positive for SARS-like CoV; farmed civet cats across the country were predominantly free of the infection (Tu et al., 2004). Thus, even the initial spread of the SARS-like CoV from bat species to civet cats (Lau et al., 2005) may have been due to human activity. The captive beluga whale that died of gammacoronavirus associated disease (Mihindukulasuriya et al., 2008) provides another possible example of human influence on the ecology of CoVs, and the possibility of a similar scenario occurring in nature. Collectively, these examples emphasize the importance of anthropogenic influences on CoV biodiversity and evolution.

Climate remains one of several important factors influencing the incidence of infectious diseases. There are multiple reviews on association of climate changes and vector-borne/water-borne diseases (Berberian and Rosanova, 2012; Dobson, 2009; Greer et al., 2008; Hales et al., 2002; Harley et al., 2011; Lafferty, 2009; Morillas-Marquez et al., 2010; Ostfeld, 2009; Patz et al., 2003; Rosenthal, 2009; Shuman, 2010; Wilson et al., 2011); however, the information for other infectious disease is insufficient. In this era of global

development and human domination in most ecosystems, climate change effects can substantially affect the ecology of CoVs and modify the extent to which humans can control and respond to the outcomes of multiple disease modifying influences. The methods of CoV transmission and their natural host reservoirs are two critical features that can be affected by climate changes. The MHV and TGEV remained infectious in sewage and water for up to 3 weeks (Casanova et al., 2009) indicating that floods can contribute to increased spread of CoVs through contaminated water sources. Additionally, BCoV was shown to survive on lettuce surfaces, retaining infectivity for up to at least 14 days (Mullis et al., 2012) demonstrating that contaminated vegetables (due to contaminated water sources) may serve as potential vehicles for CoV transmission to humans. Numerous data indicate that humidity is important for CoV survival (Casanova et al., 2009, 2010a, b; Sizun et al., 2000). A faulty sewage system, initially contaminated by the excreta of the SARS index case, with an aerosol route of transmission was suggested to be responsible for a cluster of SARS cases in 2003 in Hong Kong (Peiris et al., 2003a). Interestingly, recent experimental data revealed that MHV and TGEV survivability on environmental surfaces was greater at high (80%) or low (20%) than at moderate (~50%) relative humidity (Casanova et al., 2010b). Another study, however, demonstrated that TGEV remains viable in the airborne state at low relative humidity longer than at high (Kim et al., 2007). This indicates that both floods and extreme droughts can directly affect CoV viability and transmission. Additionally, they may affect survival or migration of wildlife species (avian and mammalian) which serve as natural reservoirs for these CoVs, imposing an indirect effect on CoV circulation and preservation. Furthermore, experimental data confirm that CoV are inactivated faster at higher temperatures: TGEV and MHV remained infectious for up to 28 days at +4 °C, while at +20 °C the viruses persisted for only 5–20 days, with the fastest inactivation at +40 °C (Casanova et al., 2010b). Therefore, global warming and subsequent droughts could negatively affect CoV survivability. On the other hand, such significant climate changes may also increase the number of and density among environmental refugees (animals as well as humans) migrating to new areas thereby creating more favorable conditions for CoV circulation, recombination and spread.

The existing data regarding seasonality of known CoVs are incomplete and sometimes contradictory. Although in temperate climates, most respiratory CoV infections in humans occur more often in the winter and spring (cold season) (Bastien et al., 2005a, b; Dowell and Ho, 2004; Vabret et al. 2005), there are data that HCoV-NL63 and HKU1 occurrence in sub-tropical (Hong Kong, China) or in humid continental (Beijing, China) climates was higher in spring, summer and fall (Cui et al., 2011; Leung et al., 2009). However, the peak infection for another human respiratory CoV, HCoV-OC43 in Hong Kong was detected in December–January (Leung et al., 2009). Interestingly, there are also variable observations on the seasonality of animal CoVs. Winter dysentery in cows occurs in winter in temperate climates, but also occurs at other times in non-temperate climates (Decaro et al., 2008b; Fukutomi et al., 1999; Park et al. 2006; Saif et al., 1991) suggesting that diverse mechanisms may promote BCoV spread in different seasons and environments. There are also data indicating that TGEV and PRCV in pigs are more prevalent in winter (Pensaert et al., 1986, 1993; Saif and Sestak, 2006) suggesting that better preservation of these viruses in frozen state in feces or at cold temperatures assists with CoV transfer. Additionally, starlings (Pilchard, 1965) and flies (Gough and Jorgenson, 1983) were indicated as potential mechanical vehicles for TGEV transmission which emphasizes that climatic changes (temperature, humidity, strong winds) can indirectly influence CoV ecology through affecting these vehicles. The PRCV appears to be airborne (Bourgueil et al., 1992; Wesley et al., 1990) traveling relatively long distances in aerosols; therefore relative humidity changes

may significantly affect its survival as was shown for other viruses (Schoenbaum et al., 1990). The report of a severe outbreak of BCoV diarrheal disease in cattle in Italy during the warmer season (Decaro et al., 2008b) suggests that in the warmer seasons, birds and insects migrating between affected herds could promote BCoV spread. For TCoV in the US, the occurrence was highest in October and this seasonality was suggested to be associated with higher humidity and the fly population rise, contributing to mechanical spread of TCoV (Cavanagh et al., 2001). Collectively, CoV circulation and spread results from an interplay of multiple factors. Fomites and mechanical vehicles are also suspected to be important for aerosol spread of human CoVs (Dowell et al., 2004; Sizun et al., 2000); therefore studies of CoV survival on fomite surfaces and mechanical vehicles in different conditions are critical. Preliminary evidence suggests that various ecological influences including climate change may have played a role in recent host range and geographic expansions of avian pathogens (Fuller et al., 2012). Thus, the increasingly recognized diversity of CoVs in migratory birds suggests that climatic change may affect their migratory pathways and therefore CoV ecology.

Whether there is true seasonality or it is variable for different CoVs and geographical regions remains to be determined. Therefore, additional research to understand the association between climatic influences and CoV spread and circulation in natural reservoirs across diverse populations and geographical regions is needed. The accumulated epidemiological data can then be used to develop predictive strategies to avert outbreaks like SARS.

21.6 CONCLUSION

Coronaviruses are a vast and important group of large RNA viruses that possess unique molecular mechanisms of transcription and recombination, providing diverse models of pathogenesis and continually emerging new pathogens. The SARS pandemic and the discovery of the remarkable variety of animal and avian as well as novel human CoVs, revealed a very complex and sustainable ecology of these viruses. Coronaviruses can persist in diverse environments, infecting a variety of avian and mammalian species. Multiple viral genes contribute to CoV pathogenesis and result in different pathogenic phenotypes depending on interaction with host responses. The observations that coronavirus tissue tropism and host range variants already exist as quasispecies during replication in tissue culture or in avian/mammalian species indicate that CoVs may shift or extend their host range leading to the emergence of new CoV variants in humans. Although influenced by anthropogenic and possibly climatic factors, CoVs respond and evolve rapidly to adapt to new hosts/tissues/environments and may even manipulate these factors to maintain their persistence and abundance. More extensive molecular epidemiologic and genetic studies are needed to develop comprehensive models to predict CoV transmission, spread and disease in relation to probable climatic changes.

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