Clinical and molecular aspects of veterinary coronaviruses

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Clinical and molecular aspects of veterinary coronaviruses

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Highlights

- Cross-species transmission is common in the family *Coronaviridae*
- Their particular replication mechanism favors the generation of new viral variants
- Coronaviruses common in veterinary science must be taken into account
- Molecular distinctive features in a viral genus are associated with pathogenesis
- Common coronavirus clinical signs must be recognized by veterinarians
- Diagnosis of animal coronavirus disease can help promote public health

Abstract

Coronaviruses are a large group of RNA viruses that infect a wide range of animal species. The replication strategy of coronaviruses involves recombination and mutation events that lead to the possibility of cross-species transmission. The high plasticity of the viral receptor due to a continuous modification of the host species habitat may be the cause of cross-species transmission that can turn into a threat to other species including the human population. The successive emergence of highly pathogenic coronaviruses such as the Severe Acute Respiratory Syndrome (SARS) in 2003, the Middle East Respiratory Syndrome Coronavirus in 2012, and the recent SARS-CoV-2 has incentivized a number of studies on the molecular basis of the coronavirus and its pathogenesis. The high degree of interrelatedness between humans and wild and domestic animals and the modification of animal habitats by human urbanization, has favored new viral spreads. Hence, knowledge on the main clinical signs of coronavirus infection in the different hosts and the distinctive molecular characteristics of each coronavirus is essential to prevent the emergence of new coronavirus diseases. The coronavirus infections routinely studied in veterinary medicine must be properly recognized and diagnosed not only to prevent animal disease but also to promote public health.

Keywords: Coronaviruses; Veterinary medicine; Clinical signs; ORFs; One health

1. Introduction:

Coronaviruses are a large group of viruses that cause disease in different animal species and humans. Animal coronaviruses cause respiratory, enteric, and neurological diseases in a wide variety of hosts, whereas human coronaviruses frequently cause mild to severe respiratory diseases that can lead to pneumonia or even death. The epidemics of Severe Acute Respiratory Syndrome virus (SARS-CoV) and Middle East respiratory syndrome virus (MERS-CoV) in 2002 and 2012 respectively were the first warning signs of coronaviruses as potential sources of zoonotic diseases. However, the 2020 pandemic of the new coronavirus SARS-CoV-2 promoted a global interest in wild and domestic animals because they are the main sources of reservoir for the recombination and transmission of the coronaviruses.

Coronavirus infections in animals are usually enzootic and it could affect certain species for long periods. Additionally, the exceptional replication mechanism and the possibility of recombination events are two main factors that may lead to cross-species transmission and enhance the zoonotic potential of coronaviruses. Therefore, the understanding of animal coronavirus infections are essential to comprehend different aspects of their ecology and evolution.

This review aims to describe thoroughly the distinctive molecular aspects, the morphology, replication and transcriptional mechanism of coronaviruses. As well as, highlighting the main clinical signs of coronaviruses infection in veterinary medicine, that affect specifically domestic, laboratory, poultry and livestock animals.

2. Classification of coronaviruses:

The family *Coronaviridae* belongs to the order *Nidovirales*, which contains 14 RNA viral families, classified based on their particular replication mechanism and genome organization. According to the recent re-classification of the International Committee for Taxonomy of Viruses (ICTV) (ICTV, 2019), the family *Coronaviridae* is now divided into two subfamilies named *Letovirinae* and *Orthocoronavirinae*. The subfamily *Letovirinae* infects amphibians and contains only the genus *Alphaletovirus*, whereas the subfamily *Orthocoronavirinae* is divided into four viral genera based on their genome structure

and phylogenetic relation: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. These four viral genera include the most relevant viral species in veterinary medicine.

3. Coronavirus structure:

The viruses of the family *Coronaviridae* are enveloped, generally spherical, with diameters of between 120 and 160 nm (Figure 1). Their envelope has characteristic projections corresponding to trimmers of the S protein, which determine the typical crown-like aspect of coronaviruses observable at electron microscopy. In the genus *Betacoronavirus*, there is also a second, smaller layer of projections formed by the hemagglutinin-esterase (HE) accessory protein (Masters, 2006). The nucleocapsid has helical symmetry composed of N protein associated with a single strand, positive-sense RNA genome ((+)ssRNA), the largest of RNA genomes (26-32 Kbp) (Lauber et al., 2013). The largest coronavirus genome is the Beluga whale coronavirus SW1, with 31686 bp in length (Mihindukulasuriya et al., 2008).

4. Genome organization and viral proteins:

The (+)ssRNA genome has a 5' capped end and a 3´ polyadenylated end, and, at both ends, there are untranslated regions (UTRs), which play important roles in viral transcription and replication (Yang and Leibowitz, 2015). Depending on the species, there are 7 to 14 open reading frames (ORFs) coding for the different viral proteins; ORF1a, 1b, S, E, M and N are conserved among different species (Figure 2) (Masters, 2006).

ORF1a and ORF1b, which are large ORFs, occupy the 5′ proximal two thirds of the viral genome and are involved in the synthesis of non-structural proteins (nsps). The processing and cleavage of these ORFs by two viral proteases generate 16 nsps, except for gamma- and deltacoronaviruses, which lack nsp1. nsp12 codifies for the RNA-dependent RNA polymerase (RdRp), a central component in the replication and transcription of the coronavirus family. Also, together with other seven nsp domains, nsp12 is used in the taxonomic classification of new virus isolates (de Groot et al., 2013; Wilkinson et al., 2020). The activity of the exoribonuclease 3´-5´ of nsp14 increases the RdRp proofreading ability, with implications in the viral mutation rates and the host immune response (Becares et al., 2016; Minskaia et al., 2006).

The remaining 3′ one-third of the viral genomes contain ORFs that encode for structural and accessory proteins. The 5´end of each ORF is preceded by a small transcription regulation sequence (TRS), a determinant factor during the transcription process.

These structural ORFs include some small ORFs that encode for nsps in some viral species, which seem not to be essential for viral replication *in vitro* (Casais et al., 2005; Hodgson et al., 2006).

The structural proteins present in the entire viral family are the S, E, M and N proteins. These four proteins are essential for the assembly and infectivity of the viral particle. The distinctive spicules of coronavirus, which are homotrimers of the S protein, are responsible for the attachment to cellular receptors (Delmas and Laude, 1990). The S protein is composed of two functional domains: S1 and S2. While S2 is relatively conserved, S1 varies among genera and even strains because it contains the receptor-binding domain and hence is responsible for cell attachment (Menachery et al., 2017). Protein E participates in assembly, release and pathogenesis, while protein M, which is the most abundant protein in the viral particle, promotes the spatial topology of viral particles by binding to the nucleocapsid (Neuman et al., 2011). Finally, protein N has two domains that interact with the RNA genome and plays a vital role as an interferon antagonist, allowing viral replication (Chang et al., 2006; McBride et al., 2014).

Depending on the genus, the genome also contains a variable number of ORFs coding for accessory proteins. Although not necessary for viral replication, accessory proteins play an important role in pathogenesis by modulating different immune proteins (Nakagawa et al., 2016, Zhao et al., 2019). In this regards, some betacoronaviruses code for a hemagglutinin esterase accessory protein called HE protein (Weiss and Leibowitz, 2011). In particular, the SARS-CoV genome contains several additional ORFs that code for eight accessory proteins that are not present in other coronaviruses (Liu et al., 2014).

5. Transcription and replication mechanism: subgenomic RNA synthesis:

The protein synthesis in coronaviruses involves a particular transcription mechanism common to all nidoviruses, which involves the transcription of nested subgenomic mRNAs (Di et al., 2018; Miller and Koev, 2000). The replicase-transcriptase complex must be synthesized from the nsps encoded in ORF1a and ORF1b. This complex is responsible for the transcription of viral subgenomic mRNA and genome replication. Once the genome is released in the cell cytoplasm, the cellular ribosomes initiate the translation of ORF1a and ORF1b. Nevertheless, as ORF1b lacks an initiation codon, ribosomal frameshifting mediated by a slippery sequence present at the end of ORF1a makes translation to continue with ORF1b (Dos Ramos et al., 2004). Consequently, both ORFs are differentially expressed into polyproteins called pp1a and pp1ab (Plant and Dinman, 2008). These two polyproteins are proteolytically processed into the individual nsps that collectively form the replicase-

transcriptase complex. This complex associates with double-membrane vesicles derived from the endoplasmic reticulum called viral factories, where negative-sense RNA will serve as template for the viral genome, meanwhile, the subgenomic mRNA will serve as template for structural and accessory proteins (Du Toit, 2020; Snijder et al., 2006).

The nested set of subgenomic mRNAs is generated by an unusual discontinuous transcription process (Miller and Koev, 2000; van Vliet et al., 2002). As mentioned, the TRS present at the 5´ end of each ORF in the 3´ genome region, called body TRS, has a complementary region in the leader region of the UTR sequence in the 5´ genome region (TRS-L). In each body TRS, the RdRp could detach and jump to the complementary TRS-L sequence, generating a variable size of a nested set of mRNAs, all with virtually the same 5´ genome sequence (Sola et al., 2005). This unique discontinuous transcription process is also the onset of recombination possibilities for all coronaviruses, leading to new viral strains (Gribble et al., 2020). Finally, all the structural and accessory proteins and viral genome synthesized are assembled in the viral factories, and the viral envelope is taken from the endoplasmic reticulum and Golgi apparatus membranes for the final release of mature viral particles by exocytosis (Garoff et al., 1998).

6. Relevant coronaviruses in veterinary medicine:

6.a Canine coronaviruses

Canine coronaviruses belong to the genera *Alphacoronavirus* and *Betacoronavirus*. The alphacoronavirus named canine enteric coronavirus (CCoV) is responsible for gastrointestinal clinical signs in puppies, whereas the betacoronavirus named canine respiratory coronavirus (CRCoV) is associated with respiratory diseases, particularly in kenneled dog populations.

CCoV is clustered in *Alphacoronavirus-1* species (subgenus Tegacovirus) with feline coronavirus and transmissible gastroenteritis coronavirus (TGEV). CCoV was first reported in 1971 during an epizootic outbreak of acute enteric disease in puppies from a military canine unit in Germany (Binn et al., 1974). This outbreak provided evidence of the importance of the fecal-oral route in CCoV transmission (Keenan et al., 1976). Since then, several outbreaks of CCoV have been reported worldwide (Costa et al., 2014; Ntafis et al., 2010; Takano et al., 2016). Comparative genetic analysis of the S gene from CCoV allows classifying CCoV into two CCoV genotypes designated CCoV-I and CCoV-II. Both genotypes, share 96% of genome identity, but CCoVI and CCoV-II only share, 54% of S protein sequence identity. The different protein S sequences are generated after recombination events with other coronaviruses (Decaro and Buonavoglia, 2008; Pratelli et al., 2003). Further,

CCoV-II is divided into two subtypes: classic CCoV-IIa and CCoV-IIb (TGEV-like CCoV), which emerged by recombination of the S gene from CCoV-II and TGEV (Decaro et al., 2009; Ntafis et al., 2011).

CCoV infections are characterized by high morbidity but low mortality. Clinical signs of CCoV infections include mild to moderate gastroenteritis, loss of appetite, vomiting, fluid diarrhea and dehydration (Pratelli, 2006). Fatal cases are usually associated with coinfections with other canine viruses as parvovirus, a common viral agent causing diarrhea in dogs (Decaro et al., 2006; Pratelli et al., 2001).

Certain virulent strains of CCoV associated with hemorrhagic diarrhea are able to kill infected puppies in a few days (Buonavoglia et al., 2006; Licitra et al., 2014). Hypervirulent strains of the CCoV-IIa subgroup called pantropic CCoV, which spread in internal organs, mainly lymphoid tissue, causing marked lymphopenia, have also been described as being responsible for the most severe course of the infection (Decaro and Buonavoglia, 2011; Pinto et al., 2014). CCoV possesses five accessory proteins (ORF3a, ORF3b, ORF3c, ORF7a and ORF7b). CCoV-I also has an additional ORF3, which provides an advantage in cell infection (d'Orengiani et al., 2015; Lorusso et al., 2008).

Molecular assays to detect CCoV in fecal samples are based on reverse transcription followed by qPCR (RT-qPCR) or nested PCR (n-PCR) assays, both targeting the M gene (Decaro et al., 2004; Pratelli et al., 1999). A multiplex qPCR has been proposed for the differentiation of CCoV and canine parvovirus (Wang et al., 2020).

Although there are several CCoV vaccines, their application is controversial. As vaccinations are usually given between 8 and 12 weeks of age and CCoV infections affect puppies less than 6 weeks old, it would be too late to prevent the illness (Day et al., 2016; Tizard, 2020).

Canine respiratory coronavirus (CRCoV), identified in the UK in 2003, is a more recent member of canine coronaviruses (Erles et al., 2003). CRCoV belongs to the genus *Betacoronavirus*, species *Betacoronavirus 1*, together with porcine hemagglutinating encephalomyelitis virus (PHEV) and bovine, equine and murine coronaviruses. Surprisingly, CRCoV has been found to be genetically unrelated to CCoV, showing only 21.2% amino acid identity in the S protein and 68.5% nucleotide identity in the RdRp (Erles et al., 2003). On the other hand, S and RdRp share 97.3% and 98.8% nucleotide identity with bovine coronavirus (BCoV) (Decaro and Buonavoglia, 2008; Erles et al., 2003). The HE accessory protein contributes to CRCoV receptor binding (Erles et al., 2007).

Several epidemiological and serological studies have demonstrated that CRCoV is one of the etiological agents involved in canine infectious respiratory disease (CIRD) in dog shelters and kennels worldwide (Maboni et al., 2019; Mitchell et al., 2017; More et al., 2020). Experimental studies of CRCoV infection in dogs from geographically distinct regions have shown signs of mild respiratory disease, including nasal discharge, sneezing and coughing (Mitchell et al., 2013). Furthermore, the infection of epithelium airways and macrophages can affect the innate immune system, allowing coinfections that could generate severe to fatal infection cases (Buonavoglia and Martella, 2007; Priestnall et al., 2009).

The diagnostic assays available for the detection of CRCoV are serological and molecular tests as RT-PCR targeted against the RdRp, HE and/or S genes, and a qPCR targeted against the N gene (Erles et al., 2003; Decaro et al., 2007; Mitchell et al., 2009; Yachi and Mochizuki, 2006). Although no vaccine against CRCoV has yet been developed, vaccination against classic CIRD-associated pathogens is known to reduce the occurrence and severity of the disease (Day et al., 2016).

6.b Feline coronaviruses

Feline coronavirus (FCoV) belongs to the genus *Alphacoronavirus*, species *Alphacoronavirus 1*. FCoV causes enteric disease in domestic cats and other members of the family Felidae (Kennedy et al., 2002; Munson et al., 2004). Based on genetic and serological studies, two serotypes of FCoV have been described: FCoV-I and FCoV-II. The main distinction between them is associated with their differences in the S gene sequence and antibody neutralization properties (Hohdatsu et al., 1991; Jaimes et al., 2020; Shiba et al., 2007; Tekes and Thiel, 2016). Serotype FCoV-I is 80-90% more prevalent than FCoV-II worldwide (Amer et al., 2012; Kummrow et al., 2005; Myrrha et al., 2019). The emergence of serotype FCoV-II has involved recombination events between the S and M genes of FCoV-I and CCoV-II (Herrewegh et al., 1998; Terada et al., 2014). According to their pathogenicity, FCoVs are divided into two pathotypes: feline enteric coronavirus (FECV), which causes subclinical or mild disease in adult cats, and feline infectious peritonitis virus (FIPV), which causes a severe enteric and systemic disease called feline infectious peritonitis (Pedersen, 2014). Rather than being separate species, FECV and FIPV are virulence variants of the same virus; in fact, it has been established that FECV can convert to a FIPV pathotype by a deletional mutation in ORF3c or by acquiring the ability to infect macrophages by varying its S protein (Rottier et al., 2005; Vennema et al., 1998). In young cats, the FECV pathotype can convert or mutate to FIPV, causing accumulation of fluids in the peritoneal area, which is known as “wet feline infection peritonitis” (Pedersen et al., 2009; Wolfe and Griesemer, 1966). Alternatively,

some infections show a less evident fluid accumulation ("dry feline infectious peritonitis") but could involve uveitis and/or neurological disorders (Stiles, 2014; Tasker, 2018).

Feline peritonitis is one of the most important infectious diseases in cats, with relatively high mortality in young cats (Pedersen, 2009). About 5–10% of FCoV-infected cats develop feline peritonitis. The disease is characterized by severe systemic inflammation, serositis and granulomatous lesions in lungs, liver, lymphatic tissues and other body cavities. FIPV macrophage infection and changes in the expression of cytokines contribute to an immune dysregulation, favoring systemic infection (Brown et al., 2009; de Groot-Mijnes et al., 2005; Kipar et al., 2006).

FCoV disease also depends on the nature of the immune response. If FCoV infection results in a cell-mediated immune response, cats will become immune. However, some cats mount an antibody immune response that contributes to the immunopathogenesis of feline peritonitis disease. The antibody-dependent response increases the virus uptake by macrophages, resulting in their activation and cytokine secretion, contributing to the production of ascitic fluid in the wet feline peritonitis disease (Perlman and Dandekar, 2005).

The natural mechanism of FCoV dispersion is the fecal-oral route. An infected animal could spread FCoVfor several weeks or even months, and a high viral shedding is correlated with feline peritonitis development. Moreover, the maternal immunity may play some role altering the course of illness in naturally infected kittens (Pedersen et al., 2008; Pedersen, 2014).

For diagnosis, indirect assays, such as immunofluorescence assay (IFA) are usually performed, but it does not discriminate between FECV and FIPV. Therefore, molecular tests as RT-qPCR or loop-mediated isothermal amplification (LAMP) PCR are used to complement the diagnosis and identify both biotypes (Herrewegh et al., 1995; Stranieri et al., 2017). A complete-decision tree according to the clinical presentation can be applied in case of suspicion of feline FIPV (Felten and Hartmann, 2019).

Vaccination against FCoV is questionable because the enhancement of the immune response increases the antibody titers, contributing to feline peritonitis (Olsen et al., 1992; Olsen, 1993). An alternative strategy is an intranasal temperature-sensitive vaccine that uses a temperature-sensitive mutant of FCoV that only replicates in the upper respiratory tract, inducing local IgA response (Day et al., 2016; Goodson et al., 2009; Olsen, 1993).

As described for canine alphacoronavirus, FCoV has five accessory proteins. The cluster of ORF3a,b,c has been shown to participate in viral pathogenesis (Haijema et al., 2004), whereas ORF7a and ORF7b are viral IFN antagonizers (Dedeurwaerder

et al., 2014). The presence of an ORF3 of CCoV-I with nucleotide deletions in cat populations could be related to the adaptation of canine strains to cat hosts (Le Poder et al., 2013).

6.c Murine coronaviruses

The two prototypic murine coronaviruses that affect the rodent family Muridae are the mouse hepatitis virus (MHV) and the rat coronavirus (RCV), both of which belong to the genus *Betacoronavirus*. MHV, a prototype of the species *Betacoronavirus 1*, was first isolated in 1947 in the USA (Cheever and Daniels, 1949). Based on their tissue tropism, strains can be clustered in polytropic/respiratory and enterotropic strains (Homberger et al., 1998). Diverse polytropic strains have an initial tropism for the nasal epithelium. After that, some strains (MHV-A59, MHV-1, MHV-3, MHV-S) spread to the liver and spleen, causing hepatitis (hepatotropic strains), whereas other strains (JHMV, MHV-4, MHV-OLB) reach the brain through neural olfactory pathways and generate a fulminant encephalopathy (neutrotropic strains) (Lane and Hosking, 2010). On the other hand, the enterotropic strains (MHV-LIVIM, MHV-DVIM, MHV-Y, MHV-RI) replicate in intestinal tissues and spread to the liver, lymph nodes of the abdomen, and, occasionally, the central nervous system (Baker, 1998; Homberger, 1997). The severity of MHV infections has been shown to be affected by the viral genotype, strain and host immune response.

MHV has been used as a suitable model to study human multiple sclerosis (Lane and Hosking, 2010), hepatitis, encephalitis, and coronavirus-cell interactions (Barthold, 1997; Compton et al., 1993; Jouanguy, 2020). MHV is highly contagious and spreads by the respiratory and fecal routes (Barthold et al., 1993). The neurovirulent JHMV strain causes fatal demyelinating encephalomyelitis, produced by necrosis and apoptosis of oligodendrocytes (Lampert et al., 1973). Some JHM strains could infect the rat brain and cause more chronic lesions (Bailey et al., 1949; Taguchi et al., 1995). The hepatotropic MHV-A59 strain causes acute hepatitis but, in some cases, can cause a persistent infection that leads to mild encephalitis (Lavi et al., 1984). Some studies have shown that this strain may lead to the production of auto-antibodies, which would in turn lead to the development of an autoimmune hepatitis (Aparicio et al., 2009; Mathieu et al., 2001). It has also been demonstrated that MHV-A59 induces optic neuritis by promoting demyelination and mixed inflammatory cell infiltration in the optic nerve (Shindler et al., 2008).

A recombinant chimeric MHV-A59 harboring the S and N genes of JHMV has been found to enhance the neurovirulence compared with the MHV-A59 wild-type strain, showing that the pathogenic phenotype is determined by its genetic composition (Cowley et al., 2010; Iacono et al., 2006; Phillips et al., 1999). The differential expression of the HE accessory

protein in JHMV but not in the MHV-A59 strain illustrates the ability of the virus to change the receptor binding specificity and cell tropism, altering the pathogenicity of murine coronaviruses (Kazi et al., 2005; Langereis et al., 2012).

The accessory ORFs in MHV (ORF2a, HE, ORF4 and ORF5a) have been demonstrated to be non-essential for cell culture replication (de Haan et al., 2002; Lai and Cavanagh, 1997; Schwarz et al., 1990). The ORF2a mutation in MHV-A59 has demonstrated that this accessory protein is an organ-specific protein, which is necessary for liver replication but is dispensable for brain replication (Roth-Cross et al., 2009). Moreover, ORF2a and ORF5a have been shown to antagonize type I interferon signaling by different mechanisms (Koetzner et al., 2010; Zhao et al., 2011).

Rat coronavirus (RCV) was first isolated in 1970 in an outbreak of respiratory disease in laboratory rat colonies (Parker et al., 1970). The prototypic strains of RCV are: Parker rat coronavirus (RCV-P) and sialodacryoadenitis virus (SDAV) (Bhatt et al., 1972). Recently, a new strain named RCV (ChRCV-HKU-24), which may represent the murine origin of *Betacoronavirus 1*, has been reported in China (Lau et al., 2015). RCV-P and SDAV are highly contagious because they can be transmitted by direct contact with infected rats, aerosols or fomites (La et al., 1992). RCV infections have high morbidity but are rarely fatal in adult rats (Percy and Barthold, 2008a).

In immune adult rats, the infections are asymptomatic or transient, but, in non-immune rats, conjunctivitis is a common sign of infection (Otto et al., 2015). RCV-P primarily replicates in the respiratory tract and lungs, contributing to necrotic lesions, and like SDAV, can cause lacrimal and salivary gland lesions (Parker et al., 1970; Percy and Barthold, 2008a).

RCV may be detected by immunohistochemistry and serological tests like IFA and ELISA, recommended for confirmation prior to exposure. Also, RT-PCR targeted to the M gene from infected tissue or feces is used to confirm active infection (Besselsen et al., 2002; Percy and Barthold, 2008a, b). Prophylactic treatment is centred in quarantine of positive colonies or even in their elimination and replacement (Nicklas et al., 2012). Nowadays, the strict microbiology checks in laboratory colonies have allowed the controlling of the prevalence of this virus agent (Pritchett-Corning et al., 2009).

6.d Bovine coronaviruses

Bovine coronavirus (BCoV), which belongs to the genus *Betacoronavirus*, species *Betacoronavirus 1*, was first reported in 1973, associated with a diarrhea outbreak in neonatal calves in the USA (Mebus et al., 1973). Since then, several BCoVs have been detected worldwide (Brandão et al., 2002; Decaro et al., 2008a; Shin et al., 2019).

BCoV is etiologically associated with respiratory and enteric disease. Respiratory signs are common in cattle of all ages, while enteric manifestations are diarrhea in neonatal calves and winter dysentery in adult cattle (Chouljenko et al., 2001; Clark, 1993; Saif, 2010; Tråvén et al., 2001). BCoV strains isolated from respiratory tracts are called bovine respiratory coronavirus (BRCoV), while strains isolated from the enteric tract are called bovine enteric coronavirus (BECoV). BECoVs can be further subdivided into BECoV-CD and BECoV-WD, referring to strains that induce calf diarrhea and winter dysentery, respectively (Boileau and Kapil, 2010). Despite their different clinical manifestation and tropism, all isolates belong to a single serotype (Ellis, 2019). BCoV has a fecal-oral and respiratory route of transmission (Clark, 1993). Fomites contaminated with BCoV are also an indirect route of transmission to livestock (Oma et al., 2018). In calves, maternal passive immunization by colostrum modulates the development of BCoV infection (Bok et al., 2018; Heckert et al., 1991).

BCoV tropism in the respiratory tract causes asymptomatic or mild disease, with fever, cough and rhinitis (Clark, 1993). However, calves of less than 6 months, transported between farms, can develop shipping fever pneumonia (Boileau and Kapil, 2010). Surprisingly, animals infected with respiratory strains could develop diarrhea due to the spread of the virus to the gastrointestinal tract via the mucus (Thomas et al., 2006). BRCoV is one of the agents involved in the multi-factorial bovine respiratory disease complex (BRDC) (Fulton et al., 2011).

As mentioned above, the enteric tropism of BCoV causes winter dysentery (WD), a disease that generates great economic losses in the dairy and meat industries. WD is characterized by acute diarrhea, depression, fever and reduced milk production in dairy cows (Clark, 1993). In turn, the watery diarrhea generated leads to metabolicacidosis and hypoglycemia (Clark, 1993; Gomez and Weese, 2017; Kanno et al., 2007).

Serological studies have indicated a variable worldwide distribution of infections, ranging from 1.71% in Argentina to more than 90% in Turkey (Bok et al., 2015; Castells et al., 2019; Yavru et al., 2016). The main seroprevalence is in beef cattle rather than in dairy cattle, so predisposition to infections is greater in early weaned calves (Clark, 1993).

BCoV has accessory proteins encoded by ORF2a, HE, ORF4 and ORF5. The deletion of the gene clusters ORF2a/HE and ORF4ab/5a has revealed that they are dispensable for virus replication in cell culture (Narayanan et al., 2014). The HE accessory protein is involved in cell entry and viral pathogenesis (Lai and Cavanagh, 1997; Langereis et al., 2012; Vlasak et al., 1988). Recombinant BCoV strains in the HE region were first described in China (Keha et al., 2019).

BCoV can be detected by means of serological tests as ELISA and immunohistochemical assays (Clark, 1993). Different variants of PCR directed to the S, M or N gene or Pan-CoV have been used in BCoV detection from nasal and fecal swabs (Amer et al., 2013; Cho et al., 2001; Decaro et al., 2008b; Gomez et al., 2017; Takiuchi et al., 2006). Multiplex PCR and qPCR have been designed for the detection of the multifactorial agents associated with BRDC (Asano et al., 2010; Kishimoto et al., 2017).

Several BCoV vaccines, whose success depends on the vaccination of animals prior to calving, so that calves will be passively immunized by the colostrum or intranasally at birth, are currently licensed (Saif, 2010; Tizard, 2020). Also, a new passive immunization strategy based on oral administration of IgY antibodies has been recently developed for the control of viral and bacterial neonatal calf diarrhea (Vega et al., 2020).

6.e Equine coronaviruses

Equine coronavirus (ECoV), which belongs to the genus *Betacoronavirus*, species *Betacoronavirus 1*, was first isolated in the USA in 1999 (ECov-NC99) from the feces of a foal with diarrhea (Guy et al., 2000) and there are reports of ECoV detection associated with respiratory and enteric disease in several countries (Bryan et al., 2019; Hemida et al., 2017; Kooijman et al., 2017; Miszczak et al., 2014; Nemoto et al., 2019; Oue et al., 2011).

The ECoV genome was completely sequenced and characterized in 2007. It has five accessory proteins: NS2, p4.7, p12.7, I and HE and a remarkable INDEL nsp3 compared with other betacoronaviruses (Zhang et al., 2007).

ECoV clinical cases are usually sporadic or epizootic and generally self-limiting in a few days with palliative supportive care. The most important ECoV route is the fecal–oral transmission, although respiratory transmission has also been evidenced, but only in experimental infections (Pusterla et al., 2018). Common clinical signs of ECoV infections are fever, depression and anorexia, and, in some cases, colic and diarrhea in adult horses (Pusterla et al., 2016). In severe cases, animals can present hyperammonemia-associated encephalopathy, which leads animals to press their head against a surface (Fielding et al., 2015; Giannitti et al., 2015). Normally, ECoV in foals is detected together with various other coinfections, whereas healthy foals experimentally infected usually develop monoinfections. This suggests that, in foals, ECoV circulates asymptomatically, explaining the unusual outbreaks in adult animals (Slovis et al., 2014). Mortality rates are generally low, although cases of

fatality rates of 27% have been detected in American Miniature horses (Fielding et al., 2015). However, a recent retrospective analysis has evidenced no fatalities in an outbreak in the same horse breed (Goodrich et al., 2020).

ECoV is diagnosed by qPCR from samples of fecal matter and nasal swabs, while detections from respiratory samples are infrequent (Pusterla et al., 2015). ECoV can also be diagnosed by a RT-LAMP PCR, which, despite its low sensitivity, is useful for epidemiological surveillance in laboratories with limited resources due to the minimal equipment required (Nemoto et al., 2015).

Although there is still no vaccine for ECoV, but since ECoV is antigenically related to BCoV, a BCoV vaccine has been used in horses, but has produced low antibody titers and no challenge studies have been done to find out whether BCoV vaccines can protect from infection in horses (Nemoto et al., 2017).

6.f Swine coronaviruses

Pigs can be infected by six coronaviruses. Four of them belong to the genus *Alphacoronavirus* (transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCV), porcine epidemic diarrhea virus (PEDV) and swine acute diarrhea syndrome-coronavirus (SADS-CoV)), whereas the remaining two are classified in the genus *Betacoronavirus* (porcine hemagglutinating encephalomyelitis virus (PHEV)) and in the genus *Deltacoronavirus* (porcine deltacoronavirus (PDCoV)).

TGEV was the first swine coronavirus discovered, in the USA in 1946 (Doyle et al., 1946). TGEV clinical signs include acute diarrhea, vomiting, anorexia and weight loss (Liu and Gerdts, 2019). The disease severity depends on the appearance of the virus as epidemic or endemic. In epidemics where the virus spreads rapidly in a swine population, TGEV affects principally newborn piglets of 2 weeks of age from naive herds. Nevertheless, infection is self-limiting (Kim et al., 2000; Saif et al., 2012). After the epidemic phase, the endemic disease is detected principally in farms with incomplete all-in all-out management or with continuous flow of naive gilts (Saif et al., 2012). TGEV can be transmitted via the fecal-oral route, fomites, and even vertical transmission through milk (Niederwerder et al., 2018; Saif et al. 2012).

A respiratory TGEV variant was reported in Belgium in 1986. This TGEV variant with a large deletion in the 5' end of the S gene was named porcine respiratory coronavirus (PRCV) (Pensaert et al., 1986). The deleted region in PRCV was responsible for the enterotropism of TGEV by recognizing sialic acid in mucins and mucin-type glycoproteins. Hence, PRCV could not be detected in the gut or intestinal mucus barrier as it occurs in TGEV infections (Schwegmann-Wessels and Herrler, 2006).

PRCV is spread via aerosol and direct contact and affects the respiratory tract, trachea, tonsils and lungs. It usually presents as an asymptomatic infection or mild respiratory disease and common clinical signs are fever, anorexia, dyspnea and polypnea (Opriessnig et al., 2011).

PRCV and TGEV share biological and antigenic epitopes in the S, M and N structural proteins. Consequently, farms infected with PRCV show a reduction in TGEV outbreaks due to the neutralizing antibodies raised against common epitopes (Decaro and Larusso 2020; Sánchez et al., 1992).

In the 1970s, another virus related to enteric disease with clinical signs similar to those caused by TGEV but detected in growing and fattening pigs was identified in Europe. This virus, which was named porcine epidemic diarrhea virus (PEDV), spread rapidly in European countries and Asia (Sun et al., 2016). PEDV transmission is by the fecal-oral route, associated with feces and vomitus contamination in the transport, feed and technical staff (Jung and Saif, 2015).

The mortality of newborn piglets from seronegative sows infected with PEDV reaches 100%, is associated with profound diarrhea and vomiting that cause extensive dehydration (Jung and Saif 2015). Phylogenetic analysis based on the S gene allows classifying PEDV strains in genogroup 1 (G1: classical strains) and genogroup 2 (G2: field epidemic or pandemic strains). The differences between both genogroups include insertions and deletions in the S gene (S INDEL) (Vlasova et al., 2014) and each genogroup is further sub-divided into subgroups: G1a, G1b, G2a and G2b (Lee, 2015). G1a includes classical strains (CV77 and cell culture-adapted and vaccine strains), G1b includes the new variant strains with the S INDEL, and G2a and G2b include the highly virulent Asian and North American strains, respectively (Lee et al., 2015). Recently, phylogenetic studies have proposed a new subgroup G2c and a new genetic classification based on the N gene (Guo et al., 2019; Kim et al., 2020). The attenuation of PEDV has been related to a large deletion in the N terminus of the S protein and with the presence of the only accessory protein ORF3 involved in replication and apoptosis in cell culture (Kaewborisuth et al., 2019; Wang et al., 2019; Ye et al., 2015).

Porcine deltacoronavirus (PDCoV) was detected in Asia in 2009, as an etiological agent of diarrhea. Five years later, it was also identified in North America and associated as the causal agent of diarrhea in pigs (Wang et al., 2014; Woo et al., 2012). While the clinical signs of PDCoV are indistinguishable from those caused by TEGV and PEDV, its mortality rate is much lower (40-50%). The main difference of PDCoV infection is that it causes important lesions in the small intestine and stomach and mild interstitial pneumonia in lungs (Ma et al., 2015).

The genome organization of PDCoV is atypical because it has only two accessory proteins (NS6 and NS7) and NS7 ORF overlaps with the N gene, a fact also observed only in avian WECoV HKU 16 deltacoronavirus (Wang et al. 2019; Woo et al. 2012).

Swine acute diarrhea syndrome-coronavirus (SADS-CoV), also known as swine enteric alphacoronavirus (SeACoV) or porcine enteric alphacoronavirus (PEAV), is considered the most recent coronavirus, emerging in China in 2016 (Gong et al., 2017; Pan et al., 2017; Zhou et al., 2018). SADS-CoV is considered the causal agent of indistinguishable acute gastroenteritis affecting pigs of all ages. Like the other enteric coronaviruses, SADS-CoV can be transmitted through the fecal-oral route. SADS-CoV shares the typical clinical signs of all enteric swine coronaviruses. Mortality rates vary from 90-100% in piglets less than five days of age to only 5% in piglets older than eight days of age (Xu et al. 2019; Zhou et al. 2018). The genome of SADS-CoV has three accessory genes named NS3a, NS7a and NS7b (Yang et al. 2020). SADS-CoV is potentially zoonotic, being a risk to human health through transmission from pigs, demonstrated by its efficiency to grow in human and monkey cell lines (Wang et al., 2019; Yang et al. 2020).

Finally, porcine hemagglutinating encephalomyelitis virus (PHEV), which belongs to the species *Betacoronavirus 1*, was isolated from brains of nursery pigs with encephalomyelitis lesions in Canada in 1962 (Greig et al., 1962). As it was later also isolated from piglets with digestive signs, the disease was named vomiting and wasting disease (VWD) (Cartwright et al., 1969). The clinical signs associated with PHEV are non-specific, characterized by an increase in the body temperature, appetite loss, lethargy and crowding together. In addition, infected pigs show seizures, weakness and fainting, as well as a dog-sitting position, and can also manifest opisthotonos and nystagmus (Gao et al., 2011; Greig and Girard, 1969; Pensaert, 2006).

In consonance with all betacoronaviruses, PHEV has a second, shorter layer of surface spikes due to the presence of the HE protein (Saif et al., 2012). The PHEV genome has a deletion of 211 nucleotides in the NS2 gene, which translates into an NS2 protein with only 194 amino acids, different from that of the other coronaviruses (Vijgen et al., 2006).

PHEV may be diagnosed by immunohistochemistry in sections of the brain, spinal cord and myenteric plexus from clinically affected animals for viral direct detection. Also, the virus can be detected in tonsils, lungs, brainstem, trigeminal ganglia and spinal cord by RT-PCR and nested PCR using specific primers for the polymerase, non-structural protein and spike protein (Mora-Diaz et al., 2019). Also, a dry room temperature stable real-time RT-PCR assay has been developed to detect PHEV from feces and oral fluids from infected pigs (Rauh et al., 2017).

Considering that porcine enteric coronaviruses cause similar clinical signs, it is necessary to use effective detection methods for their differential determination. Since molecular tests usually detect moderately conserved N and M genes (Li et al., 2019; Pan et al., 2017), pan-coronavirus PCR methods are a powerful tool to detect and differentiate between porcine coronaviruses (Fu et al., 2020).

Variations in the S gene of coronaviruses have significant effects on antigenicity. ELISA based on the PEDV S1 domain of the S protein is suitable as it does not cross-react with antibodies against other porcine enteric coronaviruses such as TGEV (and its variant PRCV) and PDCoV (Lee et al., 2011; Sun et al., 2007; Zhou et al. 2018). Besides, the antibodies against the N protein detected in some tests do not cross-react between PDCoV and TGEV/PEDV because PDCoV is antigenically different (Pan et al. 2017). Also, IgA or neutralization antibodies in colostrum or milk associated with lactogenic immunity are better markers than antibodies in serum (Bjustrom-Kraft et al., 2018).

For prevention and control of porcine enteric coronaviruses, strict biosecurity on the farms is crucial (Crawford et al., 2016). The protection against enteric disease depends on the IgA antibody titers in the intestinal mucosa. Different types of vaccines, including live, inactivated and subunit (S) vaccines for PEDV, have been developed, but their efficiency is relative and outbreaks usually occur on farms with PEDV-vaccinated pigs (Tizard, 2020). The main causes of the moderate to low effectiveness of current vaccines against PEDV are the genetic variation associated between field and vaccine strains and the recombination events in porcine coronaviruses, especially in PEDV (Lee et al., 2015). Regarding SADS-CoV and PDCoV, there are no commercial vaccines yet available. Lactogenic immunity by exposure to minced intestines from acutely infected pigs with enteric swine coronaviruses has been used as a method to decrease morbidity and mortality in porcine infections where no vaccine is available (Chattha et al., 2015; Mora-Diaz et al. 2019). Host cell pathogenesis and genes acting as virulence factors should be considered to design engineered live vaccines for porcine coronaviruses (Zuñiga et al., 2016).

6.g Avian coronaviruses

Avian coronaviruses include infectious bronchitis virus (IBV), which belongs to the genus *Gammacoronavirus*, subgenus *Igacovirus*. IBV was the first coronavirus to be discovered in history in 1931, isolated from newly hatched chicks (galliform birds) (Schalk and Hawn, 1931). It has also been detected in other galliform birds like pheasants and turkeys (Cavanagh et al., 2002; Liu et al., 2005; Miłek and Blicharz-Domańska, 2018) and from non-galliform birds like ducks (Chen et al., 2013).

IBV initially replicates in respiratory tissues, generating an acute upper respiratory disease. The respiratory lesions often increase the susceptibility to secondary viral and bacterial infections, which can lead to pneumonia, airsacculitis and peritonitis (Cavanagh, 2007; Landman and Feberwee, 2004). IBV also can infect epithelial cells in the oviduct, kidney and gastrointestinal tract, or have multiorgan tropism, associated with reduced egg production, nephrosis -typically in young birds- and proventricular infections, respectively (Albassam et al., 1986; Li et al., 2020a; Liu and Kong, 2004; Yu et al., 2001). IBV is transmitted by aerosols or direct contact with fomites. Vertical transmission is not relevant in IBV infections. The disease has a short incubation period with development of clinical signs within the 24 hours. The morbidity is usually 100% and mortality depends on the IBV strain and a variety of host factors (Jackwood and de Wit, 2020).

Numerous IBV variants with distinct serotypes and genotypes have been reported worldwide (Lin and Chen, 2017). Serotype classification involves treatment of the virus with neutralizing antibodies to analyze their cross-reactivity, whereas genotype classification comprises sequencing of the hypervariable S1 subunit from the S protein (Gelb and Jackwood, 2016; Lee et al., 2003). Considering that neutralizing antibodies are raised against the S1 region, the genetic lineages often generally correlate with the serotype variants (Kant et al., 1992). All serotypes have common epitopes in the moderately conserved sequences of the S2 subunit and M and N proteins, and only sera experimentally induced in specific-pathogen-free chickens should be used for serotype determination (Jackwood and de Wit, 2020).

Seven IBV genetic types (GI to GVII), including several viral lineages, have been described (Chen et al., 2017; Valastro et al., 2016). Like the identification of avian influenza, the different IBV strains follows the following scheme: IBV/bird type/country of origin/genetic type or serotype/strain designation/year of isolation (Cavanagh, 2001).

Nearly all commercial poultry birds are vaccinated with inactivated or live attenuated vaccines available against IBV (Jordan, 2017). Live attenuated vaccines are usually given to newborn and layer chickens (Tizard, 2020). The geographic location determines the attenuated strains used in live vaccines, for example, Massachusetts in North America, 4/91 and D274 mostly in Europe, and QX in China (Cavanagh et al., 2007; Zegpi et al., 2020).

It has been reported that a significant factor in the emergence of IBV variants globally is its viral persistence (Naqi et al., 2003). A possible explanation of long-term isolations or re-excretion of an inoculated virus is the continual cross-infection within infected or vaccinated flocks. (Bhattacharjee et al., 1995). The two main candidate sites for persistence are cecal tonsils and kidneys (Jackwood and de Wit, 2020).

The genomes of avian coronaviruses share small non-structural ORFs (3a, 3b, 5a and 5b) in the 3´genome region, which are not required for IBV replication. Manipulated IBVs unable to produce any of these ORFs can reach normal virus titers when inoculated *in vitro* (Hodgson et al., 2006). The regions in avian genomes with higher incidence of recombination breakpoints lie immediately upstream the S protein. Consequently, the emergence of new IBV strains is largely due to mutations in this protein (Jackwood et al., 2012).

IBV diagnosis requires molecular tests that amplify the S1 subunit of the S protein to determine the genetic type or viral isolation in the allantoic cavity of embryonating chicken eggs (Jackwood and de Wit, 2020). Serological tests as ELISA combined with Western Blot detecting the N protein have been useful in IBV detection (Finger et al., 2018).

Another important avian coronavirus is the turkey coronavirus (TCoV). TCoV was first identified in 1951 associated with contagious gastroenteritis in young poults (Peterson and Hymass, 1951), referred to as Bluecomb disease (Nagaraja and Pomeroy, 1997). TCoV was first related to BCoV because their N gene was 100% identical (Verbeek and Tijssen, 1991), but serological and genomic studies have shown that it is closely related to IBV (Gomaa et al., 2008; Guy et al., 1997). The S protein of TCoV and that of IBV show 34% identity (Lin et al., 2004).

TCoV has been identified in turkeys in Brazil, Canada, the USA, the UK, Italy and Australia (Brown et al., 2016; Day et al., 2014; Moura-Alvarez et al., 2013). This virus affects turkeys of all ages but clinical disease is most commonly seen in young turkeys during the first few weeks of life. Turkeys are likely the only natural hosts for TCoV. TCoV causes high morbidity, some mortality, and poor long-term growth of affected birds, resulting in significant economic losses in the turkey industry.

7. Cross-species transmission and emergence of new epidemic diseases:

Coronaviruses have a wide range of hosts, from a great variety of animals to humans. Alphacoronaviruses and betacoronaviruses have been detected mainly in mammals, gammacoronaviruses have been detected in birds and some marine mammals, and deltacoronaviruses have been detected primarily in wild birds and swine (Figure 3).

The great diversity and promiscuous host range of these viruses are components that broaden their host range, enabling them to reach humans as hosts (Woo et al., 2009). Thus far, seven coronaviruses have been identified in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2. Thus far, seven human coronaviruses have a

zoonotic origin, mainly related to bats (Corman et al., 2018; Hu et al., 2015). Nevertheless, several intermediate species have been reported in their spread and transmission (Li et al., 2020b; Raj et al., 2014, Song et al., 2005). The human alphacoronavirus HCoV-229E, for example, has an evolutionary origin related to hipposiderid bat coronaviruses, but camelids could have acted as intermediate reservoir in the transition to humans (Corman et al., 2015; Crossley et al., 2012). Regarding HCoV-OC43, which belongs to the species *Betacoronavirus 1*, a zoonotic acquisition from ungulate livestock and rodents has been widely accepted (de Groot et al., 2012; Forni et al., 2017). American tricolored bats have been proposed as reservoir origin for the alphacoronavirus HCoV-NL63 (Huynh et al., 2012), while rodents could presumably be the host reservoir for betacoronavirus HCoV-HKU1 (Hu et al., 2017). The human betacoronaviruses SARS-CoV and MERS-CoV originated in bats (Hu et al., 2017; Lau et al., 2005) and directly transmitted from civets and dromedary camels, respectively (Alagaili et al., 2014; Guan et al., 2003). Regarding SARS-CoV-2, metagenomic sequencing established a 91.02% identity with pangolin-associated coronaviruses. Hence, pangolins could be the natural reservoir but it cannot be excluded that they acquired this related SARS-CoV-2 from another animal host (Lam et al., 2020; Zhang et al., 2020).

The alignment of representative genomes from each coronavirus genus shows a whole genome identity of 54%. Non-structural proteins share a 58% identity within genera, whereas structural/accessory proteins display only 43% identity (Chen et al., 2020). This lower identity between structural/accessory proteins suggests that these proteins are involved in the adaptation of coronavirus to new hosts. Consequently, the balance between genetic conservation and diversity is crucial in the survival of coronaviruses. While the gene conservation of viral enzymes, structural proteins and spike protein S2 subunit maintain key viral functions, genetic mutations in nsps, accessory proteins and spike protein S1 subunit provide enough changes to overcome species barriers (Menachery et al., 2017).

As described above, the emergence of PRCV, a naturally occurring S gene deletion mutant of TGEV, also demonstrated the importance of the S protein in the tissue tropism of the virus. The spike protein, S1 subunit specifically, is responsible for recognition and binding to the cell receptor. Therefore, this domain seems to be essential for the extensive divergent evolution of different coronavirus species. The sequences of the S1 subunits from representative coronaviruses have been shown to vary even among the same coronavirus genus. For example, the S1 sequence of MHV shares an identity of 58% and 22% with BCoV and SARS-CoV, respectively (Li, 2012).

The exchange of the S gene of MHV with the S gene of FCoV alters the tropism of the recombinant strains that are able to replicate in feline cells (Haijema et al., 2003). Another example is the translocation of the S gene from a non-pathogenic to a pathogenic IBV, which changes the tropism of the virus (Casais et al., 2003). The difference in receptor binding observed between respiratory and enteric gammacoronaviruses seems to be due to the 64% difference between their S1 domains (Ambepitiya Wickramasinghe et al., 2015).

Generally, accessory proteins, which are able to antagonize the host immune response, influence the pathogenicity of coronaviruses (Liu et al., 2014; Michel et al., 2020; Rabouw et al., 2016; Totura et al., 2012). The coronavirus hemagglutinin-esterase accessory protein, for example, could be involved in the promiscuousness of BCoVs in dogs and humans (Saif, 2004). Also, the murine HE has been identified as responsible for the change in receptor specificity, altering organ tropism (Langereis et al., 2012).

The large RNA genome of coronaviruses allows certain degree of modifications. The characteristic replication cycle and the synthesis of subgenomic mRNAs increase the possibility of homologous recombination and mutations of different coronavirus strains, facilitating the potential of interspecies spread (Su et al., 2016; Woo et al., 2009).

Nevertheless, not all are changes in the coronavirus genome. The replicase transcription complex has the most conserved non-structural proteins (nsp3, nsp5, nsp 12-16), which serve as species demarcation among coronaviruses (Carstens, 2010). On the other hand, the M and N proteins are the most conserved structural proteins (Neuman and Buchmeier, 2016). The cross-reactivity among TGEV, PRCV, FIPV, CCoV and SARS-CoV indicates conservation of epitope/s on the N protein within these viruses (Sun and Meng, 2004).

Interspecies transmission of coronaviruses has been repeatedly demonstrated: canine to feline (Patrelli et al., 2003); canine and feline to porcine (Woods et al., 1981; Woods and Wesley, 1992); porcine to foxes and dogs (Saif and Sestak, 2006); and avian vaccine attenuated strain to wild birds (Hughes et al., 2009). Interestingly, betacoronaviruses, commonly found in mammals, have been identified in cloacal and tracheal swabs from Brazilian wild birds, commonly infected with gammacoronaviruses (Durães-Carvalho et al., 2015). This interspecies transmission is an advantage for the virus, but at a high risk for the host.

8. Conclusions:

The exceptional number of coronaviruses carried by different hosts, the high plasticity in the viral receptor, the particular replication mechanism and the continuous modification of animal habitats are ingredients that favor interspecies transmission. The latent threat of animal coronaviruses cross-species transmission has been recently demonstrated in the 2020 pandemic of SARS-CoV-2.

Preventing the occurrence of zoonotic infections requires maintaining barriers between natural reservoirs and the human population. Clinical signs and molecular distinctive features in diagnostic methods in coronavirus infection, in domestic, livestock or even laboratory animals (supplementary data) must be taken into account by veterinary medicine to prevent animal diseases and, consequently, promote public health.

Author contributions

Conceptualization: Metz GE; writing original draft preparation: Colina SE, Serena MS, Echeverría MG, Metz GE; writing review & editing, Metz GE; figure editing, Colina SE, Metz GE.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of interest

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Figure 1: Scheme of a betacoronavirus particle. The membrane contains: the S protein (~150 kDa), which forms prominent spikes on the viral surface and gives the name to this viral family; the E protein (~8-12 kDa), which is found in small quantities; the M protein (~25-30 kDa), which is a small transmembrane and most abundant protein in the viral particle; and the HE protein (~45-65 kDa), which is a glycosylated protein with acetyl-esterase activity present only in most betacoronaviruses, which forms another small layer of projections in viral particles. The nucleocapsid contains the N protein (~43-55 kDa), which is a phosphorylated ribonucleoprotein associated with the RNA genome.

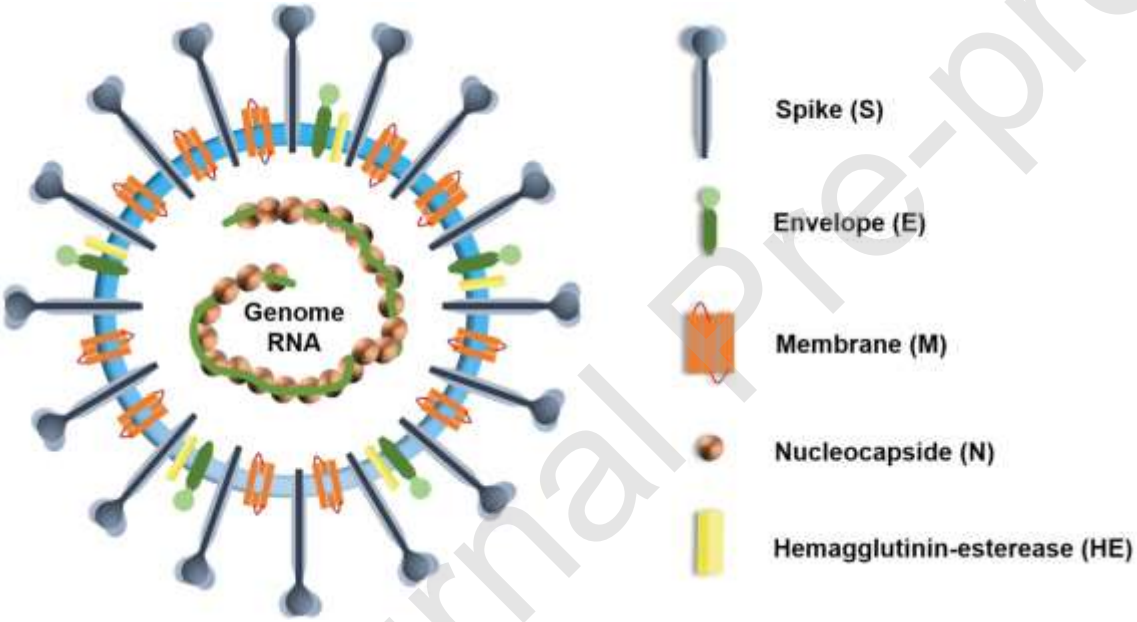

Figure 2: Genomic structure of representative animal species from the four coronavirus genera. In all coronaviruses, the genomes (~27-33 kbp) are organized into 5′ non-structural ORFs (ORF1a and ORF1b), which are two-thirds of the genome, and 3′ structural and accessory ORFs. Representative coronavirus genomes in veterinary sciences include: alphacoronaviruses, represented by feline infectious peritonitis virus (FIPV) (NCBI Reference Sequence: NC_002306.3); betacoronaviruses, represented by murine hepatitis virus (MHV) (NCBI Reference Sequence: NC_048217.1); gammacoronaviruses, represented

by avian infectious bronchitis virus (IBV) (NCBI Reference Sequence: NC_001451.1), and deltacoronaviruses, represented by porcine coronavirus HKU15 strain HKU15-155 (GenBank: JQ065043.2).

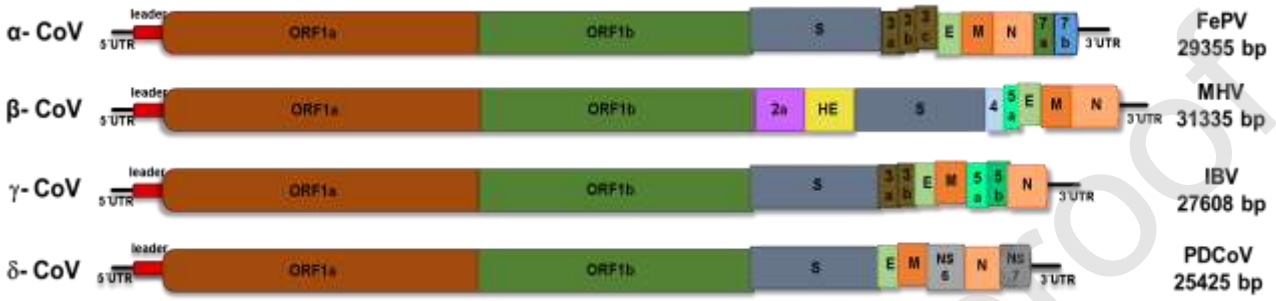

Figure 3: Representative image of the diversity of animal species where coronaviruses have been identified. For more extensive information related to coronaviruses detected in each animal species:

Alphacoronaviruses:

https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Tree&id=693996&lvl=3&lin=f&keep=1&srchmode=1&unlock

Betacoronaviruses:

https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Tree&id=694002&lvl=3&lin=f&keep=1&srchmode=1&unlock

Gammacoronaviruses:

https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Tree&id=694013&lvl=3&lin=f&keep=1&srchmode=1&unlock

Deltacoronaviruses:

https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Tree&id=1159901&lvl=3&lin=f&keep=1&srchmode=1&unlock