CORONAVIRUSES: THERE AND BACK AGAIN

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SUMMARY

With the raise of SARS-CoV-2 in late 2019 and the associated COVID-19 pandemics, much of the knowledge gathered from decades on research on other coronavirus species that use humans and other animals as hosts is invaluable to help counteract the burden of this new disease. This review aims to bring the highlights on coronavirus Biology and the most frequent diseases they might cause, serving rather as an introduction to the field.


INTRODUCTION

Coronaviruses are all but new viruses: their origin dates back to 293 million years ago (WERTHEIM et al., 2013), in the Permian. Nor are they any novelty to the Veterinary field, as a host of coronavirus species is found in practically any mammals and birds of both domestic and wild origins.

Bats are hosts to a high diversity of current coronaviruses and allowed the evolution of the major branches of these viruses. Find new coronaviruses in bats should come with no surprise either.

Human coronaviruses have also been around for a while, arguably for hundreds of thousands of years (BRANDÃO, 2018). Common cold coronaviruses (HCoV-OC43 and HCoV-229E) and those involved in other respiratory diseases in humans (HCoV-HKU1 and HCoV-NL63) are ubiquitous and cause seasonal infections, year after year.

SARS-CoV-1 and MERS-CoV were detected in 2002 and 2012, respectively, and were associated to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which caused short-lived pandemics; SARS has not seem anymore, while MERS is restricted to the Middle East now.

But by November 2019, bats, humans and coronaviruses made ground for a new chapter of coronaviruses history, one as previously never seen: COVID-19 (coronaviruses disease 2019) caused by SARS-CoV-2 that possibly came from Rhinolophus affinis in the Chinese territory (ANDERSEN et al., 2020). This virus rose from the East and spread to the West, causing millions of infections and hundreds of thousands of human deaths.

A high affinity for the human receptor ACE2 (angiotensin-converting enzyme 2), a long incubation period that allowed for cryptic transmission and the multisystemic symptoms, way beyond any flu-like symptoms, accounted for the burden SARS-CoV-2 is now for Public Health.

In the meanwhile, it became clear how the basic aspects of coronaviruses were unknown even amongst some virologists and how the general public was eager for more information of these tricky viruses and the diseases associated to these.

This article brings a collection of summarized information of coronavirus Biology and the diseases caused in the most common domestic animals, as well as concerns in Public Health, to serve as an introduction rather than an extensive review.

Taxonomy

Coronaviruses belong to the order Nidovirales (Riboviria: Orthornavirae: Pisoniviricota: Pisoniviricetes), family Coronaviridae, subfamily Orthocoronavirinae; given their genetic and antigenic diversity, they are divided into four genera: Alphacoronavirus (14 subgenera), Betacoronavirus (5 subgenera), Gammacoronavirus (3 subgenera) and Deltacoronavirus (WONG et al., 2019; ICTV, 2020). In addition, they can affect different hosts, with Alpha and Beta infecting mammals (including humans), while Gamma and Delta are detected in birds and some non-human mammals (WOO et al., 2012; CUI; LI; SHI, 2019).

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Molecular biology

Coronavirus shows an enveloped, crown (corona)-like virion of circa 120nm in diameter and of one ring shape, with a total mass of 18 x 10^-17 g (CAVANAGH, 2007). The genome is a positive-sense, single-stranded linear RNA of up to 32kb, with a set of genes arranged in a nested pattern which are structurally polysictronic but functionally monocistronic, all expressed after the transcription of gene-specific subgenomic to genomic size mRNAs; two untranslated regions (UTRs) are found in the genome, being one at the 5' and one at the 3' extremes of the genome (MASTERS, 2006).

The most 5' 2/3 of the genome, the ORF1ab, code for the replicase, a set of 15 to 16 non-structural proteins (nsps) with a role in RNA transcription and replication and regulation (MASTERS, 2006; ZIEBUHR, SNIJDER, 2007).

Walking downstream on the genome, one can find the gene for the hemmaglutinin-esterase gene (HE) in some betacoronaviruses as the Bovine coronavirus BCoV, with a role as a secondary attachment protein (MASTERS, 2006).

The spike gene codes for the spike glycoprotein S, found as a trimer emerging from the virion though the envelope; S is cleavable in S1 and S2 in some coronaviruses by either trypsin-like or furin-like proteases (the case of SARS-CoV-2), what makes this protein activated for virus binding by the subunit S1, the outermost one. Subunit S2 after cleavage by a different cleavage mechanism has its fusion site activated, allowing the fusion of the viral envelope with the endosomal membrane after virus entry (CAVANAGH, 1983; LAI; CAVANAGH, 1997).

Next comes the envelope E protein, with a major role on virion structure, together with the membrane M protein (MASTERS, 2006; MO et al., 2013). At the last gene on the 3' end is the nucleocapsid N gene, a phosphorylated protein with the endosomal membrane after virus entry (CAVANAGH, 1983; LAI; CAVANAGH, 1997).

Replication at a glance

Once the viron enters the cytoplasm via a clarithin-mediated endocytosis, the fusion domain in S2 leads to the fusion of the envelope to the endosome and the acidification inside the endosome results in virion disassembly, allowing the positive-sense genomic RNA to associate to free and rough endoplasmic reticulum-associated ribosomes, the result being the translation of the polyprotein replicase, which is co-translationally cleaved by nsps 3 and 5, releasing all functional nsps.

Of the core RNA transcription and replication processes, nsp12, the RNA-dependent RNA-polymerase RdRp will rule them all. This nsp binds to specific secondary structures on the 3' UTR, starting the transcription of a negative version of the RNA, but it might stop at the transcription regulating sequences (TRS) found in the intergenic regions if it will find them. Upon encountering a TRS, RdRp undocks from the template RNA and redocks to the TRS close to the leader sequence at the 5' end of the genome; but this undocking might happen at any of the TRSs stochastically.

The result is that a set of negative-sense sub genomic set of RNAs will be produced, each corresponding to one ORF. These negative subgenomic RNAs will then serve as templates to the RdRp, resulting in positive sense correspondents, which now include not only sub genomic mRNAs but also genome-size mRNAs, which are the genomic RNA; eventually the ribosomes will bring them all to translation (HOLMES; LAI, 1996; LAI; CAVANAGH, 1997; MASTERS, 2006).

All replication takes place in the cytoplasm. Virion assembly begins with the association of multiple copies on f N to the genomic RNAs synthesized as aforementioned; upon contacting N monomers, the genomic RNA will bind them and shape to the helicoidal symmetry.

M protein monomers in the Golgi or endoplasmic reticulum then dock to the nucleocapsid, making a covering layer to which E also associated; fully mature virions are found in the cytoplasm after budding though the Golgi membrane saturated with S protein trimers. Fully mature virions accumulate inside vesicles and then leave the shadows of the cell via exocytosis, without lysing the cell (BRANDAO; LOVATO; SLHESSARENKO, 2012).

The expression of cytoskeleton proteins is increased during coronavirus cycle, resulting in reorganization of the cytoplasm into “nests” of virus protein synthesis and accumulation in an environment that is protected for the virus; increased expression of superoxide dismutase and heat-shock proteins might lead to immune-induced lesions (CAO et al., 2012).

All proteins but N shall not pass to the cell nucleus; once inside the nucleus, N and also the leader RNA cause the p53 apoptotic protein to be redistributed on the cytoplasm, delaying apoptosis, besides decreasing cell DNA synthesis, arresting cell cycle at the G2/M phase due to a lower cyclin expression. In this manner, Golgi and endoplasmic reticulum degeneration is prevented; as these are sites form viriongenesis, virus cycle is enhanced: coronaviruses stabilishd an apparent fellowship with the cell, but with advantages for the virus only (CHEN et al., 2002; DOVE et al., 2006).
**Bovine coronavirus**

Bovine coronavirus BCoV (*Betacoronavirus 1*) occurs as a unique serotype and some geographically-specific lineages (BRANDÃO et al., 2006) and is able to infect the respiratory and enteric tract of bovines.

In calves, BCoV is one of the main causes of neonatal calf diarrhea and might be acquired by either respiratory or oral routes. Upon infection on the respiratory tract, BCoV might lead to respiratory disease and a secondary enteritis might result after ingestion of exsudate containing the virus. On the other hand, the oral route leads directly to enteritis.

In adult bovines, BCoV is the cause of seasonal epizootic dysentery, also known as winter dysentery, a manifestation that might occur during peaks of either high or low temperatures that lead to immunosuppression and a lower amount of IgA on the enteric lumen. Outbreaks last for about 10 days and the regression of clinical signs is spontaneous, but 10% of lactating cows might be affected and take weeks to recover milk production levels.

A BCoV vaccine is available in combination with rotavirus A and K99 *Escherichia coli* as inactivated formulations, used to vaccinate pregnant cows and thus improve maternal immunity via Colostrum.

**Swine coronaviruses**

The most recently discovered coronavirus of the swine is the Swine Acute Diarrhea Syndrome Coronavirus SADS-CoV, first reported in 2017 in China (reviewed by YANG; YU; HUANG, 2020), which, together with the Transmissible gastroenteritis virus (TGEV, *Alphacoronavirus 1*) and Porcine Epidemic Diarrhea Virus (PEDV) are the alphacoronaviruses that use the enteric tract of swine as an environment and might be a cause of concern for diarrhea in pigs; Porcine respiratory coronavirus (PRCoV) is a variant of TGEV able to replicate in and cause disease of the respiratory system of swine. Porcine hemagglutinating encephalomyelitis virus (PHEV) is a betacoronavirus that primarily infects the upper respiratory tract of swine and migrates to the central nervous system, resulting in tremors, opisthotonus, vomiting and wasting disease and death (MORA-DÍAZ et al., 2019). Porcine deltacoronavirus is also and enteric virus of swine that might lead to enteritis and vomiting and poses a threat to swine health (HE et al., 2020).

**Canine coronaviruses**

Canine coronavirus (CCoV) and Canine respiratory coronavirus (CRCoV) are known to infect dogs. CCoV, TGEV and Feline coronavirus (FCoV) are intimately related when it comes to evolution: CCoV-I shows a divergent spike protein and an extra gene at ORF3, of which vestiges can be found in CCoV-II and TGEV and it has been suggested that a recombination between CCoV and a unknown coronavirus led to the emergence of CCoV-II (LORUSSO et al., 2008).

CCoV belongs to the species *Alphacoronavirus 1* (Alphacoronavirus: Tegacovirus) (DECARO; BUONAVOGLIA, 2011) occurs as serotypes/genotypes I, IIa and IIb that, upon enteric infection in puppies, might lead to enteritis of a minor clinical importance. Nonetheless, a highly virulent lineage of CCoV-IIa emerged that is pantropic and highly lethal to puppies (BUONAVOGLIA et al., 2006; PINTO et al., 2014). These pantropic CCoV now must be taken into account on when the importance of the inactivated vaccines given to young dogs against CCoV is discussed.

Canine respiratory coronavirus – CRCoV (*Betacoronavirus: Embeccovirus: Betacoronavirus 1*) (SZCZEPANSKI et al., 2019) was first reported in the UK in 2003 and is currently considered as a part of the Canine infectious respiratory disease (CIRD) together with Canine parainfluenzavirus, Canine adenovirus 1 and 2, Influenzavirus, *Bordetella bronchiseptica* and *Mycoplasma* ssp (DECARO et al., 2016; MITCHELL et al., 2017; MABONI et al., 2019). This is a virus closely related to BCoV and HCoV-OC43 with nucleotide identities of 97.3 e 96.9%, respectively (SZCZEPANSKI et al., 2019), but with no reports of current spillovers.

**Feline coronavirus**

Feline coronavirus (FCoV) belongs to species *Alphacoronavirus 1* (ICTV, 2020) and is a ubiquitous pathogen of domestic cat populations worldwide. FCoVs are classified into two types, type 1 (most frequently) and type 2 (HOHDATSU et al., 1992; BENETKA et al., 2004; LAUZI et al., 2020), based on the genetic and antigenic difference of their S protein (SHIBA 2007). FCoV type 2 arose following recombinant events between FCoV type 1 and CCoV (HERREWEGH et al., 1998). Both types occur as two pathotypes, feline infectious peritonitis virus (FIPV) and feline enteric coronavirus (FECoV), that can be distinguished by their biological behavior. Hypotheses of the intrahost (internal mutation theory) and interhost (high virulent-low virulent FCoVs) origins of FIPV are accepted (PEDERSEN et al., 2009; CHANG; EGBERINK; ROTTIER, 2011; HORA et al., 2013; JAIMES et al., 2020).

FIPV is highly virulent and responsible for the highly fatal disease feline infectious peritonitis (FIP) that occurs in domestic (PEDERSEN, 2009; KIPAR; MELI, 2014) and wild felids (PEARKS WILKERSON et al., 2004; STEPHENSON et al., 2013), whereas FECoV typically causes asymptomatic infections or in some circumstances result in a mild, self-limiting gastrointestinal disease in domestic cats (PEDERSEN, 2014). FECoV is widespread among the feline population: in multi-cat environments nearly 100% of cats that get in contact with FECV from feces of shedding cats become infected(ADDIE et al., 2000; SHARIF et al., 2009), and up to 10% of FCoV infected cats may develop FIP (PEDERSEN, 1976; ADDIE; JARRETT, 1992).

Specific mutations or a combination of mutations in S, 3abc and 7ab FCoV genes fundamentally trigger the tropism switch from
enterocytes to macrophages, change pathogenicity and lead to the FIP development (CHANG et al., 2012; PEDERSEN et al., 2012; LICITRA et al., 2013; BANK-WOLF et al., 2014; BORSCHENSKY; REINACHER, 2014; DEDEURWAERDER et al., 2014; PORTER et al., 2014; HORA et al., 2016).

The manifestations of FIP has been classified into two forms: an effusive (wet) FIP characterized by vasculitis and polyserositis inducing thoracic and/or abdominal effusions, and a non-effusive (dry) FIP characterized by piogranulomatous lesions in organs (PEDERSEN, 2014).

FCoV is an extremely challenging virus for feline medicine; besides FIP being fatal, there are difficulties in FIP diagnosis, especially in dry form, as laboratory and clinical findings are unspecific and the two pathotypes are indistinguishable by several diagnostic methods. But give to the hypothesis that only FIPV but not FECoV is able to spread systemically, it makes sense that detection of high viral loads of FCoV RNA in effusion or any other body fluid or tissue except for the gastrointestinal tract (LONGSTAFF et al., 2017; TASKER, 2018) combined with clinical pathological manifestations compatible with the disease indicates presence of the virulent pathotype FIPV.

There is a vaccine commercially available in available in the USA and in some European countries, however it is not recommended by the vaccination guidelines of class associations, due low level of protection (SCHERK et al., 2013; DAY et al., 2016).

Experimental antiviral treatments have been reported, but only adenosine nucleoside analogue GS-441524 appears to have any therapeutic potential (MURPHY et al., 2018; DICKINSON et al., 2020). However, further studies on this antiviral nucleoside analogue are still needed so that it can be approved by controlling agencies and may be instituted as a treatment.

Avian coronaviruses

Avian coronavirus AvCoV (previously known as IBV, Avian infectious bronchitis virus), Avian coronavirus 9207 and Duck coronavirus are the three species of gammadacoronaviruses, a classification based on the amino acids identity of the most conserved non-structural proteins (ICTV, 2020).

Avian coronavirus has a wide host range that includes different types of wild birds like ducks, geese, pelicans, seagulls etc) (HEPOJOKI et al., 2017), synanthropic birds like pigeons (CAVANAGH, 2005) and poultry (turkeys, chickens and quail)(VILLARREAL et al., 2007; TORRES et al., 2013; YAGHOUBI et al., 2019).

The first coronavirus reported in the world was the causal agent of infectious bronchitis virus (IBV) which belongs to Avian coronavirus in 1936, this caused respiratory disease in broilers (BEACH; SCHALM, 1936), an agent that have high morbidity and could affect the poultry industry in all stages, causing economic losses in all levels (CAVANAGH, 2005, 2007).

AvCoV virus replicates not only in tracheas and lungs, but also in in the Harder glands, esophagus, lungs, Bursa of Fabricius, duodenum, ileum, cecum, rectum, kidneys and reproductive tract (CAVANAGH, 2005, 2007) leading to decreased growth, infertility and egg drop, with a significative economic burden to the poultry industry (COLVERO et al., 2015).

The spike protein is the main antigenic determinant for AvCoV and serves as a basis for antigenic and genetic serotyping and genotyping, respectively. Six genotypes (I to VI) and 34 lineages (VALASTRO et al., 2016; CHEN et al., 2017; LI et al., 2020). Lineage GI-11 predominates amongst poultry population in Brazil and is widespread in the country.

A number of inactivated and attenuated AvCoV vaccines is available for poultry; despite the 20% to 25% nt and 50% aa differences in the spike (LACHHEB et al., 2017), a sufficient level of cross-protection might be achieved by the combination of two different lineages (DE WIT; COOK; VAN DER HEIJDEN, 2011).

Importance for Public Health

Human coronaviruses (HCoVs) have been detected worldwide, with mild symptoms as cold (flu-like), with or without diarrhea.

All HCoV have zoonotic origin and ancestry with high genetic and antigenic similarity with coronaviruses of bats and/or rodents. And generally presenting intermediate hosts (HI), responsible for spillover, also of non-human origin.

Seven are the HCoV strains, divided into: Alphacoronavirus (HCoV-229E and HCoV-NL63) with ancestry in bats (DONALDSON et al., 2010; HUYNH et al., 2012; CORMAN et al., 2015, 2016; TAO et al., 2017); and Betacoronavirus (HCoV-OC43 and HCoV-HKU1) from rodents (CUI; LI; SHI, 2019), plus three related to bats (SARS-CoV-1, MERS-CoV and SARS-CoV2).

The importance of emerging viruses, mainly of zoonotic origin, is well understood in the history of coronaviruses; until 2002 only two HCoVs were known (HCoV-229E and HCoV-OC43). From this, and less than two decades later, five new coronaviruses were detected, three of them of pandemics, betacoronaviruses with bat-strains similarity (FORNI et al., 2017; YE et al., 2020).

HCoV-229E

The HCoV-229E virus (Alphacoronavirus), isolated in 1966-7, has bats (Hipposideros sp.) as ancestor hosts (CORMAN et al., 2015).

Alpacas (Vicugna pacos) are reported as intermediate hosts (CROSSLEY et al., 2010; CORMAN et al., 2015); other viral strains such as HCoV-229E-like have already been reported in dromedary camels, but their participation in the infection cycle for humans has not yet been fully established (CORMAN et al., 2016).

It’s hardly distinguished from influenza A or rhinovirus infections, presenting mild upper respiratory symptoms (colds) and may present associated diarrhea,
HCoV-OC43

OC43 (lineage A) is responsible, together with HCoV -suggesting as hosting in rodents and cattle (CUI; LI; 2011) a putative ancestor for HCoV-OC43 has been available in the worldwide databases (LAU et al., 2010).

Despite being its intermediate host is unknown, it was associated with bats (Perimyotis subflavus) (ABDUL-RASOOL; FIELDING, 2010; HUYNH et al., 2012).

A study in Kenya observed the circulation of HCoV-NL63 in Triaenops afer bats with specific protein derived from HCoV-229E, which circulates in another bat species (Hipposideros sp.), showing a chimeric protein that might have contributed to their ability to infect humans (TAO sp., 2017).

Phylogenetic analyzes showed similarity to the HCoV-229E virus, however there is still a divergence in its recombination sequence, such as the use of different cell entry receptors, since HCoV-NL63 uses an angiotensin-1 converting enzyme 2 (ACE2), while HCoV-229E uses an N-aminopeptidase (HUYNH et al., 2012; MILEWSKA et al., 2017; TAO et al., 2017).

HCoV-NL63

Another worldwide alphacoronavirus is HCoV-NL63, isolated in 2004 from a seven-month-old child with symptoms of cold, conjunctivitis and bronchiolitis (FIELDING, 2011; SU et al., 2016).

In addition, HCoV-NL63 is divided into eight genotypes (A-H) (ZHU et al., 2018), and the demonstration of high genetic and antigenic similarity, suggesting that BCoV went through a process of recombination sequence, such as the use of different cell entry receptors, since HCoV-NL63 uses an angiotensin-1 converting enzyme 2 (ACE2), while HCoV-229E uses an N-aminopeptidase (HUYNH et al., 2012; MILEWSKA et al., 2017; TAO et al., 2017).

HCoV-OC43

Within the Betacoronavirus genus, HCoV-OC43 (lineage A) is responsible, together with HCoV-229E, for 10-30% of winter colds in the world, and may also cause gastroenteritis and necrotizing enterocolitis (VIJGEN et al., 2005b, 2005a; GAUNT et al., 2010).

Though only a few complete genomes is available in the worldwide databases (LAU et al., 2011) a putative ancestor for HCoV-OC43 has been suggesting as hosting in rodents and cattle (CUI; LI; SHI; 2019).

HCoV-OC43 and bovine coronavirus (BCoV) demonstrate high genetic and antigenic similarity, suggesting that BCoV went through a process of “jumping between hosts” allowing infection in humans, and it cannot be the other way around, due of 290 -nucleotides deletion in the gene HCoV-OC43 in relation to BCoV (VIJGEN et al., 2005a).

In addition, HCoV-OC43 is divided into eight genotypes (A-H) (ZHU et al., 2018), and the attachment of the spike protein to the host cell carried out by the 9-O-acetylated sialic acid receptor.

HCoV-HKU1

In 2005, HCoV-HKU1 was isolated from a 71-year-old patient with pneumonia and bronchiolitis from Hong Kong, China (WOO et al., 2005b).

Like the other HCoVs described, HCoV-OC43 has a worldwide distribution with clinical manifestations ranging from self-limiting to severe cases of infections in the lower respiratory system, associated or not with gastroenteritis (VABRET et al., 2006; SU et al., 2016).

Showing rodents coronaviruses as ancestors and an unknown intermediate-host (YE et al., 2020), HCoV-OC43 belongs to lineage A of the genus Betacoronavirus, encoding hemagglutinin-esterase (HE) an extra envelope protein (WOO et al., 2005a, 2005b; HUANG et al., 2015; SU et al., 2016).

SARS-CoV-1

Severe Acute Respiratory Syndrome-related coronavirus - SARS-CoV-1, was first detected in Guangdong, China (2002) (PEIRIS et al., 2003). It is a lineage B Betacoronavirus related to atypical pneumonia ('ground glass'-pattern), flu-like symptoms and rapidly impairment of the lower respiratory system, the patients needing mechanical ventilation in 20-30% of cases(DE WIT et al., 2016). In addition, it can also affect the nervous, renal and hepatic systems (ZHAO, 2007; PERLMAN; NETLAND, 2009).

With a mortality rate of 9%, cases of SARS-CoV have been reported in 27 countries, totaling more than 8,000 cases and 775 deaths, the elderly being more susceptible (SU et al., 2016).

Its aggressiveness is related to human-to-human aerosol transmission and to SARS-CoV-1 receptor in the host cell, the angiotensin converting enzyme 2 (ACE2) (LI et al., 2003), due to its presence in the lungs and the loss of function of these organs (KUBA et al., 2005; ZHAO, 2007).

Possibly originated in a wild animals market by the commercialization of live wild animals (PERLMAN; NETLAND, 2009; GE et al., 2013; SU et al., 2016) SARS-CoV-like virus (SARSr-Rh-Bat CoV) was detected in horseshoe bats (Rhinolophidae family) (LI et al., 2005; FORNI et al., 2017).

Serological and virological surveys in chinese ferret-badgers (Melogale moschata), raccoon dogs (Nyctereutes procyonoides) and masked-palm civets (Paguma larvata) indicate this last species as an important viral incubator and intermediate host (GUAN et al., 2003; TU et al., 2004; ZHAO, 2007).

Many other SARS-CoV-like were isolated from bats in China (LAU et al., 2005, 2010; LI et al., 2005; GE et al., 2013; YANG et al., 2016), Europe (DREXLER et al., 2010), Africa (TONG et al., 2009) and North America (DOMINGUEZ et al., 2007).

MERS-CoV

Initially described as HCoV-EMC (Erasmus Medical Center), the Middle East respiratory syndrome coronavirus (MERS-CoV) was isolated from a 60-year-old patient with kidney failure and pneumonia in Saudi Arabia (ZAKI et al., 2012).

MERS-CoV is classified as Betacoronavirus (Lineage C), having similarity to bat coronaviruses HKU4 and HKU5 (Tylonycteris and Pipistrellus, respectively) (LAU et al., 2013; Vesperillionidae, Molosidae, Nycteridae, Neoromicia and Emballonuridae) bats have already been reported with MERS-related CoVs (COTTEN et al., 2013a, 2013b; MEMISH et al., 2013; CORMAN et al., 2014).

Eventually, dromedary camels (Camelus dromedarius), were identified as intermediate hosts,
with anti-MERS-CoV antibodies detected in samples back from 1992 (ALAGAILI et al., 2014; MEYER et al., 2014; REUSKEN et al., 2014).

In a meta-analysis carried out by Badawi & Ryoo (2016) verified the severity of the condition is related to the patient’s previous/chronic comorbidities, showing patients having diabetes and/or hypertension, cardiorespiratory problems, obesity, among others.

During the epidemic, 2012-13, more than a thousand infected were reported and mortality rate of 30-40% (BALKHY et al., 2016). The transmission has been related to family clusters and health agents (RAJ et al., 2014).

Unlike SARS-CoV, the cell receptor used by MERS-CoV is CD26 or DPP4 (dipeptidyl peptidase 4), expressed in kidney, intestine, liver and prostate (RAJ et al., 2013). The symptoms start as the other coronaviruses with fever, cough, breath difficulty, vomiting diarrhea, and rapidly evolution to pneumonia (“ground-glass”pattern), encephalitis, myocarditis, kidney disease and need the for mechanical ventilation (THE WHO MERS-COV RESEARCH GROUP, 2013).

From 2014-18, over a thousand cases of MERS were reported, despite the trend of decreasing cases and mortality (DONNELLY et al., 2019) related to the fastest diagnosis and measure of supportive therapy with antivirals, antibiotics, antiprotozoal agents, chloroquine, convalescent serum and corticosteroids (MO; FISHER, 2016), and the development of vaccine (DU et al., 2013).

SARS-CoV 2

By the end of December 2019, SARS-CoV2 was identified from the Huanan Seafood Market, Wuhan (China) (HUANG et al., 2020).

With approximately 50% genome identity with MERS-CoV, and 82% with SARS-CoV-1 (CHAN et al., 2020) sharing the same ACE2 receptor (CHAN et al., 2020; MOUSAVIZADEH; GHASEMI, 2020; SHANG et al., 2020), SARS-CoV-2 is classified as Betacoronavirus (lineage B; subgenus Sarbecovirus) (ICTV, 2020).

Its ancestry was attributed to the Bat-CoV RaTG13 (from *Rhinolophus affinis* with which SARS-CoV-2 shares 96.2% genome identity (ZHOU et al., 2020). Ferrets, cats, dogs, and other domestic animals are being tested for susceptibility to SARS-CoV-2 (SHI et al., 2020). However, to date, the closest candidate for and intermediate host is the pangolin (*Manis javanica*) that hosts a coronavirus with 85-92% identity with SARS-CoV-2 (LAM et al., 2020).

SARS-CoV-2 is easily transmitted from person to person via aerosols, saliva droplets, and possibly via fecal-oral route (AMIRIAN, 2020; WU et al., 2020; XIAO et al., 2020; XIE; CHEN, 2020).

Patients might be asymptomatic, what favors SARS-CoV-2 dissemination fever, cough and dyspnea as initial symptoms and the clinical course might be moderate or worsen to pneumonia and severe decreased breathing capacity. Critical cases are those needing care in an intensive care unit due to acute respiratory syndrome and extensive pulmonary impairment, shock and organ failure, with a high lethality in these cases (GAO et al., 2020; HUANG et al., 2020; XIE; CHEN, 2020).

All ages can be affected, but patients above 60 years old and those with previous comorbidities (hypertension, diabetes and cardio-respiratory diseases) have a trend to present more severe conditions (YANG et al., 2020). Loss of taste and smell (GAUTIER; RAVUSSIN, 2020), conjunctivitis (HONG et al., 2020), Kawasaki syndrome in children (JONES et al., 2020) are some of the secondary symptoms associated with COVID 19.

To date, there are no commercial vaccines available or a definite treatment protocol. One the other hand, there is a great debate about the efficiency of Chloroquine, which *in vitro* was able to inhibit viral entry (WANG et al., 2020), but *in vivo* it does not show efficiency, and may even worsen ventricular arrhythmias (MEHRA et al., 2020).

Countries have been establishing protocol suggestions for the treatment of patients with mild or severe symptoms, combining antivirals (lopinavir and ritonavir, remdesivir), anticoagulants, corticosteroids, antibiotics, antiprotozoal agents, and the use of mechanical breathing (KHAN et al., 2020; LI; DE CLERCQ, 2020; ZHANG et al., 2020).

Approximately 6.3 million people tested positive for SARS-CoV-2, with 380,000 deaths on all continents, until June 3 (WHO, 2020). Despite the constant recommendation of the World Health Organization (WHO) for mass testing, there is a diagnostic deficiency, leading to underestimation on the real numbers of the disease (GAO et al., 2020; MARCEL et al., 2020; WHO, 2020; ZITEK, 2020).

The prevention of SARS-CoV 2 must be carried out by the use of individual protective masks, given the high number of viral particles in the upper respiratory system (GAO et al., 2020); measures of social isolation and distancing between people (1-2 meters) to limit dispersion (SINGHAL, 2020), cleaning objects/surfaces (JIANG et al., 2020), as well as frequent personal hygiene and hand washing, with products that degrade the viral envelope, such as soap and/or 70% ethanol (SINGHAL, 2020).

**CONCLUDING REMAKS**

Coronaviruses have a long history that balances between a very peaceful relationship with their hosts and a fearful outcome such as the most recent human coronavirus related to COVID-19. The accumulated understanding on coronavirus diseases in non-human animals is a precious source of knowledge to help prevention, treatment and control of COVID-19.

A continued survey for coronaviruses in wildlife, mainly bats, will shed light on a further and perhaps more worrisome question: Which is the next coronavirus?
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