Acta virologica **65**: 264 – 267, 2020 doi: 10.4149/av_2020_215

Coronaviruses

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Received April 2, 2020; accepted April 6, 2020

Summary. – The members of coronavirus family are facultative pathogens of birds and mammals, including men. From their first isolation 60 years ago, they caused smaller or larger epidemics mainly originating from China. The most recent pandemic quickly spreading worldwide has affected over 2,000,000 people.

Keywords: coronavirus; epidemic; single strand vRNA

The family *Coronaviridae* comprises large enveloped viruses (80–120 nm in size) containing a relatively long single strand of RNA of positive polarity, which consists of 27–32 x 10^3 nucleotides. It probably represents the largest known viral RNA (vRNA) molecule (*1, 2*). Coronaviruses were first identified in early sixties, when samples from sick poultry (showing symptoms of infectious bronchitis), piglets and/or calves (the latter showed signs of severe diarrhea) were inoculated into tissue cultures and afterwards examined by electron microscopy. Based on serologic differences between the isolated strains as well as on their genome phylogeny, coronaviruses were divided into four genera designated Alpha-, Beta-, Delta-and Gamma-coronavirus (*3, 4*). Of the four described coronavirus genera, alpha- and beta-coronaviruses are believed to originate from bat species, whereas gamma- and delta-coronaviruses might be of avian origin (*5*). All the five previously known human coronaviruses belong to genera alpha-coronavirus (HCoV-229E and HCoV-NL63) or beta-coronavirus (HCoV-OC43, HCoV-HKU1 and SARS-CoV), respectively.

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[1]The number of COVID-19 positive individuals in the meantime has exceeded over 2,000,000.

Abbreviations: CoV = coronavirus; COVID-19 = coronavirus disease 2019; IBV = infectious bronchitis (virus); MERS = Middle East Respiratory Syndrome; PED(V) = porcine epidemic diarrhea (virus); SARS = Severe Acute Respiratory Syndrome

The name of the viral family in question comes from the typical shape of virions, whose envelope has globe-like protrusions about 20 nm in diameter, reminding of the sun crown. The first two isolates mentioned above (229E and OC42) seemed relatively low pathogenic, rarely causing mild symptoms of upper respiratory tract infection similar to common cold and/or some sneezing. The isolates from the previous epidemic in the Guangdong province in China, which suddenly emerged in November 2002, spread quite rapidly, affecting over 3,500 individuals and resulting in 182 deaths (5.0%). Some of these coronavirus isolates were recognized to cause a new respiratory disease termed „Severe acute respiratory syndrome" (SARS). The SARS strains were isolated not only in several Chinese provinces including the capital city of Beijing, but also in Singapore and in neighbor countries (*6*). Together 129 sequence variations were detected among the 14 randomly sequenced SARS virus RNAs, revealing 16 recurrent variants, which could be attributed to geographical origin of the isolates (such as Hong-Kong, Singapore and Beijing).

In contrast to the relatively low pathogenic classical SARS strains, the recently reappearing coronavirus isolates coming from the Chinese city of Wuhan behaved differently, when eliciting interstitial pneumonia with occasional lethal outcome in a relatively high proportion of infected subjects. The novel isolates have been later on designated Coronavirus 2019, i.e. COVID-19 (*7, 8*). They spread more rapidly as compared to the SARS virus, causing the recent global life-threatening epidemics worldwide. On 12th January 2020, the World Health Organization (WHO) named the above-mentioned intersti-

tial pneumonia as coronavirus disease 2019 (COVID-19). The Coronavirus Study Group (CSG) of the International Committee has proposed an official name for the new coronavirus, i.e. SARS-CoV-2 (*9*). According to the European Centre for Disease Prevention and Control (ECDC), since 31st December 2019 until 20th March 2020, together 242,488 cases of COVID-19-positive individuals have been reported, including 9,885 deaths. Within next 6 days, according to the same agency, a total of twice as many (exactly 467,710) cases have been reported, including 20,947 deaths. Within additional 4 days, i.e. by March 30th, an incredible number of 741,914 infections along with 35,337 deaths (4.8%) has been registered.

Noteworthy, some of the coronavirus-associated diseases and syndromes had been described already before the Second World War, i.e. at times when the causative agent had been unknown. As shown in Table 1, many coronavirus species are pathogenic for non-human mammals as well as for birds (*10*). Thus, coronaviruses appear to be important pathogens in veterinary medicine as well. While the most frequent mammalian and bird coronaviruses cause respiratory tract infections, some of them may be responsible for gastrointestinal and/or neural disorders including gastroenteritis, hepatitis and/or meningoencephalitis (*11*).

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in humans in 2012 (*12*). In this epidemic, dromedary camels were found to be the only documented zoonotic source for humans. The clinical findings in this Middle Eastern respiratory syndrome (MERS) have been described and reviewed in great detail (*13, 14*). The incubation period for MERS ranged from 5 to 7 days, but in some cases, it lasted up to 12 days (*15*). Fever, cough, shortness of breath, and pneumonia (with abnormal chest radiography) were the most frequently noted symptoms. In addition, myalgia, diarrhea, vomiting, abdominal pain, chills or rigors, or malaise were seen (*16, 17*). Renal or pulmonary failure and a relevant shock

Table 1. Overview of coronaviruses and related diseases

Virus	Antigenic group	Localization of lesions				
		Respiratory tract (RT)	Gastrointestinal tract	Liver	Central nervous system	Other
Human coronavirus 229E	I (alpha)	Upper RT infection	None	None	None	None
Transmissive gastroenteritis virus (TGEV) in pigs		None	Gastritis, enteritis	None	None	None
Canine coronavirus (CCoV)		None	Gastritis, enteritis	None	None	None
Porcine respiratory coronavirus (PRCoV)		Upper RT infection	None	None	None	None
Porcine epidemic diarrhoea virus (PEDV)		None	Gastritis, enteritis	None	None	None
Feline enteritis coronavirus (FeCoV)		None	None	None	None	None
Feline infectious peritonitis virus (FIPV)		Pneumonia	Peritonitis	Hepatitis	Meningoencephalitis	Fasting syndrome
Human coronavirus NL63		Upper RT infection	None	None	None	None
Human coronavirus OC43	II (beta)	Upper RT infection	None	None	None	None
Murine hepatitis virus (MHV)		None	Gastritis, enteritis	Hepatitis	Meningoencephalitis	None
Calf coronavirus		None	Gastritis, enteritis	None	None	None
Human coronavirus SARS (severe acute respiratory syndrome virus)		Tracheobronchitis, interstitial pneumonia	Gastritis, enteritis	None	None	None
Human coronavirus 4408		Upper RT infection	None	None	None	None
Human coronavirus HKU 1		Upper RT infection	None	None	None	None
Porcine hemagglutinating encephalomyelitis virus (HEV)		Upper RT infection	None	None	Meningoencephalitis	None
Middle Eastern respiratory syndrome coronavirus (MERS)		Upper RT infection	None	None	None	None
Bat coronavirus (BCoV)		Upper RT infection	None	None	None	None
Infectious bronchitis virus (IBV, avian)	III (gamma)	Tracheobronchitis	None	None	None	Nephritis (urate deposits)
Bluecomb virus (turkey coronavirus, TcoV)		None	Gastritis, enteritis	None	None	None

syndrome were also described to represent possible complications in severe and/or fatal cases (*18*).

Several coronaviruses infect domestic animals such as pig, cat and/or poultry. Divergence of these coronaviruses is driven by genetic recombination events. Out of those, which infect-pigs, especially the porcine epidemic diarrhea (PED) virus may be of interest, since it elicits a highly contagious enteric disease of swine, featured by acute vomiting, dehydration, and watery diarrhea (*19*). The first PED virus (PEDV) outbreak was documented in the United Kingdom in 1971 (*20*), from where it spread to other European countries (prototype strain PEDV CV777). Between 2010 and 2013 severe outbreaks of PED were reported in China; they were caused by an emerging highly virulent PEDV strain (*21*). Most recently, an aggressive porcine epidemic diarrhea outbreak has occurred in a swine fattening farm in the province of Teramo, Abruzzi region, Italy (*22*). The S (spike) protein of PEDV, similarly to that of human coronaviruses, is one of the most critical functional proteins that contribute to apoptosis of affected intestinal epithelium cells (*23*). PEDV as well the transmissible gastroenteritis virus (TGEV) replicate in enterocytes of the small intestine and are the causative agent of a fatal diarrhea in newborn piglets (*24*). TGEV is a coronavirus similar to PEDV, causing diseases characterized by vomiting, diarrhea, and death from severe dehydration in piglets, resulting in huge losses to the swine-breeding industry worldwide. Both viruses establish the infection of enterocytes in the small intestine, and their spike (S) proteins play a key role in the virus-cell binding process. Under conditions, when the large intestine is filled with a thick layer of mucus, proteases and sialic acid, and the pH is rather low, the coronavirus replication is considerably enhanced (*25*).

Another important non-human coronavirus is the avian infectious bronchitis virus (IBV), which causes an acute and highly contagious upper respiratory disease leading to substantial economic losses to the poultry industry worldwide, when affecting not only the respiratory tract, but also inducing nephritic syndromes and decreased egg production (*26*). This virus replicates not only in the epithelium of upper and lower respiratory tract tissues, but also in many tissues along the alimentary tract and elsewhere, e.g. kidney, oviduct and testes. It can be detected in both respiratory and fecal material (*27*). There is increasing evidence that IBV can infect species of birds other than chicken. The simultaneous emergence of IBV strain variants can attribute to their recombination. Although IBV belongs to the distant Gamma-coronavirus group, similarly to other coronaviruses, its S glycoprotein contains several epitopes involved in infectivity that play an essential role in virus attachment to the susceptible host cell (*28*). The mutations in S protein undoubtedly have a selective advantage; generally speaking, immunity poorly protects against heterologous serotype infection (*29, 30*). Here again, the S protein is the major inducer of virus-neutralizing (VN) antibody protection. Due to the genomic and antigenic variability of IBV and poor vaccine protection, the characterization of emerging IBV strains based on genotype and serotype is critical for preventing IB disease. The newly emerging virus variants may not respond to the vaccines currently in use. Nevertheless, vaccination in order to control IB (at least in part) has been practiced for over 50 years using both live and/or inactivated vaccines, including subunit vaccines containing the S1 spike antigen determinant. Following infection with a live IBV vaccine strain there was a good primary IgM response. In addition, it has been shown that cytotoxic T-cell (CTL) responses correlated with initial decreases in clinical signs. Interferon was detected in trachea and lung, and at lower levels in plasma, kidney, liver and spleen (31).

Taken together, the human coronavirus strains as well as all the non-human coronaviruses are facultative pathogens causing disease in about 25–30% of infected individuals. The lethality is approximately similar, thus, from the total of positive cases tested, in about 6 % the disease may have a lethal outcome. The novel coronavirus has become a real challenge not only for the hospital personnel but also for the public healthcare and its responsible administration.

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