Novel coronavirus (SARS-CoV-2) epidemic: a veterinary perspective

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The current threatening highly pathogenic pneumonia outbreak is caused by a novel coronavirus (CoV) named SARS-CoV-2. This name was given by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses, which is responsible for developing the official classification of viruses and taxonomy of the *Coronaviridae* family (Gorbalenya *et al.* 2020). Instead, the disease that SARS-CoV-2 causes has been named by the WHO as COVID-19. This novel epidemic emerged in December 2019 in Wuhan City, Hubei Province, China and continues to expand. Epidemiological investigations revealed that many initial patients were exposed to wildlife at the Huanan seafood wholesale market (South China Seafood Market), which is the largest seafood market in central China, and where different species of bats, minks, snakes, Chinese bamboo rats, but also cats of different breeds, porcupines, dogs, poultry and other farm animals are commonly sold. These markets are known as 'wet markets' since they are traditionally places that sold dead and live animals out in the open and where blood and other body fluids originating from different animal species represent an exceptional source for the spread of infectious diseases and the jump of species barriers by pathogens. Since 1st of January 2020 the South China Seafood Market has been closed by the Wuhan Municipal Government. To date (February 11th, 2020) Chinese health officials have reported 42,708 cases of infections with SARS-CoV-2 in China, including 10,980 cases outside of Hubei Province. A total number of 395 infections with SARS-CoV-2 also are being reported in other countries (24) internationally (WHO, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=fb6d49b1_2). Remarkably, human-to-human transmission has been evidenced. So far, the virus killed 1,017 individuals in China and 1 in the Philippines. China responded quickly by informing the World Health Organization (WHO) of the outbreak and sharing sequence information with the international community after discovery of the causative agent (www.gisaid.org). This permitted the assessment of several molecular methods for rapid SARS-CoV-2 diagnosis. SARS-CoV-2 has been also rapidly isolated in permissive cell-culture.

CoVs were not considered to be highly pathogenic to humans until the outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and 2003 in Guangdong province, China, lately spread on a global scale (Zhong *et al.* 2003, Drosten *et al.* 2003, Fouchier *et al.* 2003, Ksiazek *et al.* 2003). Ten years after SARS-CoV, another highly pathogenic coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia and other Middle Eastern countries (Zaki *et al.* 2012). The evidence that SARS-CoV and MERS-CoV were transmitted directly to humans from masked palm civets (*Paguma larvata*) and dromedary camels, respectively, (Guan *et al.* 2003, Alagaili *et al.* 2014, Hemida *et al.* 2013), and that both viruses are thought to have originated in bats (Cui *et al.* 2013, Hu *et al.* 2017, Lau *et al.* 2013) led to the hypothesis that also SARS-CoV-2 may be of animal origin.

CoVs act as primary actors within the so-called human/animal interface across which a plethora of infectious pathogens has been observed to emerge, jump species barriers and eventually evolve, thus finding new ecological niches and causing new epidemiological phenomena. Before the emergence of SARS- and MERS-CoV, four human CoVs (HCoVs), namely HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1 were known to infect humans, mostly causing mild infections (eg common cold) in immunocompetent people. Interestingly, low pathogenic CoVs have also their ancestors in animals. Based upon the current available genomic sequences, bats are thought to be the natural hosts for HCoV-NL63 and HCoV-229E, rodents for HCoV-OC43 and HKU1. Coronaviruses needed intermediate hosts (cattle for HCoV-OC43 and alpacas for HCoV-229E) before being able to infect humans, as it was the case of SARS-CoV and MERS-CoV with masked palm civets and dromedary camels, respectively (Cui *et al.* 2019).

CoVs are enveloped positive-strand RNA viruses with exceptional genetic complexity and variety. One major contributing factor to CoV diversity is high-frequency RNA recombination (Banner *et al.* 1991, Lai *et al.* 1985, Makino *et al.* 1986). New sero- and biotypes have arisen from homologous RNA recombination, i.e., the exchange of corresponding sequences among related CoVs (Brian *et al.* 1997, Herrewegh *et al.* 1998, Jia *et al.* 1995, Kottier *et al.* 1995), while heterologous RNA recombination events with non-coronaviral donor RNAs have led to the acquisition of novel genes (Luytjes *et al.* 1988, Snijder *et al.* 1991, Zeng *et al.* 2008). SARS-CoV is paradigmatic of these evolutionary mechanisms as it emerged through recombination of bat SARS-related coronaviruses (SARSr-CoVs). Recombination of SARS-CoV in the spike (S)-protein gene, which recognizes cell surface receptors, might have mediated the initial cross-species transmission event from bats to other mammals. If, on one hand a direct progenitor of SARS-CoV was not found in bats, on the other, all its genomic elements were identified in bats present in one single cave of Yunnan province, China (reviewed in Cui *et al.* 2018). SARS-CoV-2 is genetically close to SARS-CoV (Gorbalenya *et al.* 2020) and it has been proposed that SARS-CoV-2 is also a recombinant virus. There is a certain evidence that SARS-CoV-2 originated from recombination between a bat SARS-like CoV and a coronavirus of unknown origin. Additionally, it

has been proposed that snake is the most probable wildlife animal reservoir for the SARS-CoV-2 based on the virus relative synonymous codon usage (RSCU) bias, which is closer to that of snake compared to other animals. Truth to be told, neither SARS-CoV-2-like sequences nor elements of its genome have been evidenced in snakes so far (Ji *et al.* 2020). Researchers in Guangzhou, China, have suggested that pangolins (gen. *Manis*, Linnaeus 1758), long snouted, ant-eating mammals often used in traditional Chinese medicine, are the probable direct animal source of SARS-CoV-2 for humans. This suggestion originated from the detection of CoVs closely related to SARS-CoV-2 in pangolins. However, caution is needed and genetic analyses are currently ongoing (https://www.nature.com/articles/d41586-020-00364-2). Importantly, the CSG also clearly evidenced that SARS-CoV-2 clusters with SARS-CoVs within the species *Severe acute respiratory syndrome-related coronavirus* of the genus *Betacoronavirus* (Gorbalenya *et al.* 2020). SARS-CoV-2 has been assigned to an existing species of hundreds of known viruses largely isolated from humans and bats. These viruses have names derived from SARS-CoV, but only the viral isolates originating from the 2002-2003 outbreak have been confirmed to cause SARS in humans. Thus, the reference to SARS reflects the phylogenetic grouping rather than linking this virus to a specific disease (i.e., SARS) in humans. Moreover, it is important to point out that SARS-CoV-2 is not a descendent of SARS-CoV (Gorbalenya *et al.* 2020).

CoVs are well-known to veterinary virologists since decades. Taxonomically, they are members of the subfamily *Orthocoronavirinae* in the family *Coronaviridae* and the order *Nidovirales*. This subfamily consists of four genera *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. The alphacoronaviruses and betacoronaviruses infect only mammals. The gammacoronaviruses and deltacoronaviruses infect birds, but some of them can also infect mammals (Cui *et al.* 2018). Most of the breakthrough studies on strictly veterinary CoVs of the past century focused on mouse hepatitis virus (MHV), feline infectious peritonitis virus (FIPV) and infectious bronchitis virus of poultry (IBV). Nowadays, porcine epidemic diarrhea virus (PEDV) causes severe gastroenteritis in young piglets, leading to significant morbidity, mortality, and ultimately economic losses (Wang *et al.* 2019). Porcine hemagglutinating encephalomyelitis virus (PHEV) mostly leads to enteric infection but can also infect the central nervous system, causing encephalitis, vomiting and wasting in pigs (Mora-Diaz *et al.* 2019). Recently the novel swine acute diarrhea syndrome coronavirus (SADS-CoV) has been described in pigs (Wang *et al.* 2019). CoVs are also a common cause of enteric (canine enteric coronavirus, CCoV type I and II) and respiratory (canine respiratory coronavirus, CRCoV) disease in dogs (Decaro and Buonavoglia 2008). The key role of veterinary virologists in the field of discovery, viral evolution, genome manipulation and pathogenesis studies of CoVs has been highlighted over recent years. It has been indeed proposed that type I CCoVs and FCoVs evolved from a common ancestral virus, and that the canine and feline type II lineages arose from multiple recombination events with an unidentified genetic source (Lorusso *et al.* 2008). CCoV-II has been recognized as the ancestor of transmissible

gastroenteritis virus of swine (TGEV) (Lorusso *et al.* 2008) and, interestingly, back recombinant CCoV-IIs harboring the S protein 5'-end of TGEV have been also described in dogs (Decaro *et al.* 2009). CRCoV likely originated from bovine coronavirus (BCoV), the direct ancestor of human HCoV-OC43 (Lorusso *et al.* 2009). Porcine respiratory coronavirus (PRCoV) is a deletion mutant of its parental enteric TGEV but with respiratory tropism (Pensaert *et al.* 1986, Bernard *et al.* 1989, Rasschaert *et al.* 1990); genomic sequences highly similar to PEDV were detected also in bats and SADS-CoV is a recent spillover from bats to pigs (Zhou *et al.* 2018). FCoV type I and II cause a mild or asymptomatic enteric infection in young cats, but during persistent infection, specific mutations in the S protein (Chang *et al.* 2012) may transform the virus into a highly virulent strain of FCoV (FIPV), that leads to the development of a lethal disease known as feline infectious peritonitis (FIP) (Chang *et al.* 2011, Haijema *et al.* 2007, Pedersen *et al.* 2009).

The emergence of SARS-CoV-2 is paradigmatic of the strict relationship existing between human and animal health, ecosystem condition and human habits. It is accepted that many viruses have existed in their natural reservoirs for a very long time. The constant spillover of viruses from their natural hosts to humans and other animals is largely due to human activities, including modern agricultural practices and urbanization. Therefore, the most effective way to prevent viral zoonosis is to maintain the barriers between natural reservoirs and human society, in mind of the 'One Health' concept. Nevertheless, all recent human health hazards were caused by zoonotic agents. But how worrisome a particular zoonotic disease is? Is it possible to prioritize zoonotic diseases? To answer these questions, authorities should take into account the potential of a given disease to cause a pandemic, how severe can be the impact on humans and animals, and whether the disease is listed as a potential agent of bioterrorism. In all cases, the role of veterinarians is crucial. Veterinarians operate in the veterinary public health (VPH) system, a major part of public health in which human health and well-being are the central tasks. Remarkably, veterinary virologists operating in VPH coordinate virus surveillance and pathogenesis studies in domestic animals and wildlife, a crucial aspect in trying to understand the etiology of viral zoonoses, their impact on individual health as well as on populations over time, but also for preparedness for human emerging diseases. In this perspective, the combination of innovative novel diagnostic technologies, including next-generation sequencing, and big data management within VPH institutes, represents the first line of defense for human health. Reasonably, a new generation of veterinarians is warranted by the current needs of the society. This can be obtained through a profound revolution of veterinary schools teaching programs. Bioinformatics, genomics, statistics, ecology, social sciences and communication are fundamental skills for the veterinarians of the next future that will face next pandemic of animal origin.

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