

February 12, 2020

A novel coronavirus was discovered in Wuhan, China, in December of 2019. It has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Gorbalenya, 2020), formerly known as 2019-nCoV, and the resulting disease is named COVID-19 (World Health Organization, 2020). This InfoSheet compiles information on the human-animal interface for this and related viruses.

Virus

- Coronaviruses are enveloped, positive-sense, non-segmented, single-stranded RNA viruses, and members of the *Coronaviridae* family in the *Nidovirales* order. They are classified into four genera containing viruses pathogenic to mammals:
 - *Alphacoronavirus*: including Porcine Epidemic Diarrhea virus (PEDv), transmissible gastroenteritis virus (TGEV), swine acute diarrhea syndrome coronavirus (SADS-CoV), canine enteric coronavirus, feline enteric coronavirus, feline infectious peritonitis virus (FIPV)
 - *Betacoronavirus*: including severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2, Middle East respiratory syndrome coronavirus (MERS-CoV), murine hepatitis virus (MHV), bovine coronaviruses, rat sialodacryoadenitis virus, porcine hemagglutinating encephalomyelitis virus, canine respiratory coronavirus, equine coronavirus
 - *Gammacoronavirus*: mainly occur in birds, including infectious bronchitis, and also a coronavirus isolated from a captive beluga whale
 - *Deltacoronavirus*: relatively recently discovered; also occur mainly in birds, but have also been found in pigs
- The SARS-CoV-2 was sequenced on January 3, 2020. Three strains have been identified, and they are in the 2b lineage of the *Betacoronavirus* genus, *Orthocoronavirinae* subfamily (Figure 1). Alignment of these strains' full genomes and other available genomes of *Betacoronavirus* showed the closest relationship with bat SARS-related coronaviruses (SARSr-CoV) (Identity 88-96%) from Horseshoe bats (*Rhinolophus affinis*) (Wenjie et al., 2020; World Organisation for Animal Health, 2020; Zhou et al., 2020). The sequence is 79.5% identical to SARS-CoV (Zhou et al., 2020), and 50% to MERS-CoV (Lu et al., 2020).
- Within the genus *Betacoronavirus*, SARS-CoV and SARS-CoV-2 both fall into the subgenus *Sarbecovirus*. Three distinct clades have been identified in this subgenus, including:
 - Clade 1: bat SARSr-CoV strains from Bulgaria and Kenya
 - Clade 2: SARS-CoV-2 and bat SARSr-CoV strains from eastern China
 - Clade 3: SARS-CoV and bat SARSr-CoV strains from southwestern China (Lu et al., 2020)

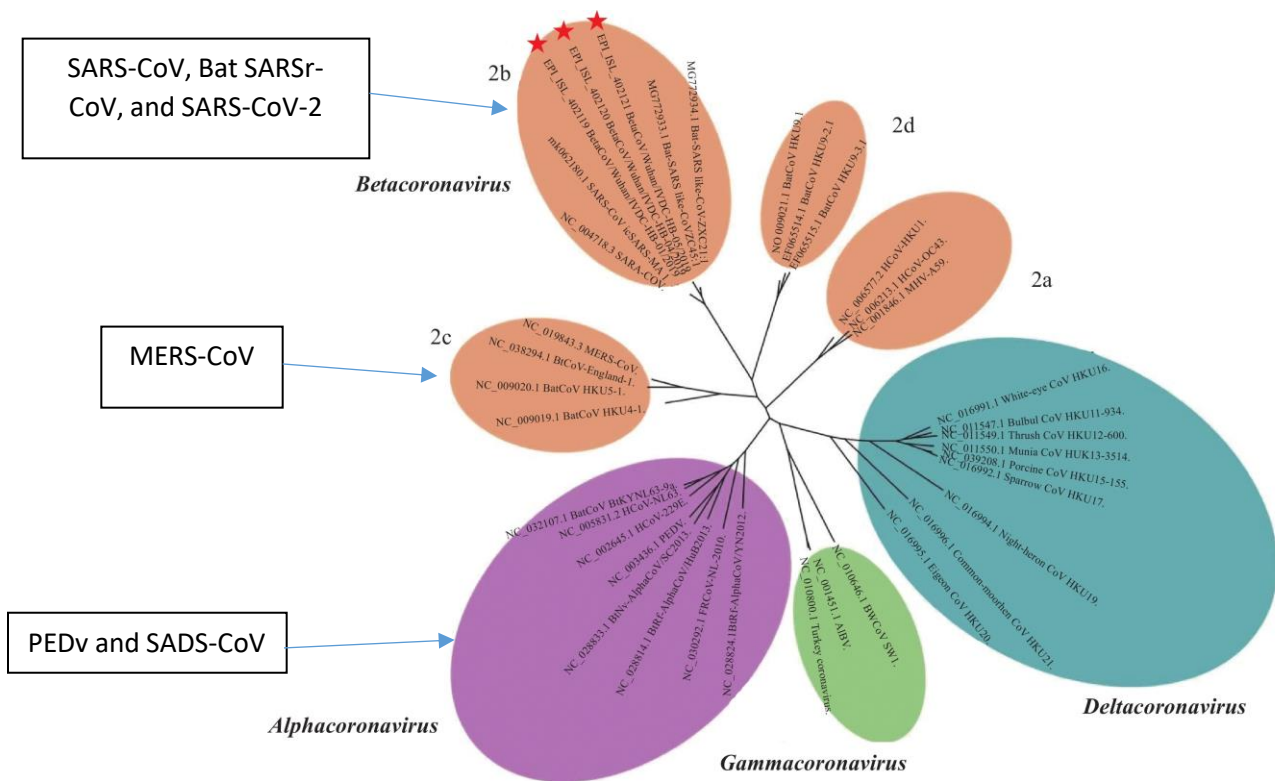


Figure 1: Phylogenetic relationships among coronaviruses (Wenjie et al., 2020).

Mutation and Recombination

- Coronaviruses have moderate to high rates of mutation, with average substitution rates of approximately 10^{-4} substitutions per year per site (Su et al., 2016).
- Recombination occurs when two or more similar viruses infect the same cell, and it can result in genetic changes of the progeny virus that might result in an effect on host range, virulence, evasion of host immunity, and resistance to antivirals. Although 'reassortment' requires a segmented viral genome, such as influenza virus, other methods of 'recombination' can occur with non-segmented viruses (Simon-Loriere & Holmes, 2011).
- This appears to occur frequently with viruses in the family *Coronaviridae*. For example, research on another *Betacoronavirus*, MHV, showed that up to 25% of the progeny of co-infected cells were found to be recombinant. When Haijema et al. (2003) injected cat cells with FIPV and added a gene fragment from the spike protein of MHV, the exchange of the feline spike gene with the mouse spike gene took only several hours and the resulting recombinant virus was infectious to mouse cells, not cat cells. The high rates of recombination are caused by the strategy of gene expression used by coronaviruses, which is called discontinuous transcription and specifically relies on the template-switching property of the RNA-dependent RNA polymerase (Simon-Loriere & Holmes, 2011).

- The most frequent recombination breakpoints for SARSr-CoVs are within the genes encoding the spike (S) protein, which contains the receptor-binding domain, and an accessory protein (Cui et al., 2019).
- Based on studies of SARS-CoV and the angiotensin converting enzyme-2 (ACE2) receptor, it appears that very few amino acid substitutions would be required for adaptation to a homologous receptor of a new host species (Holmes, 2005; Li et al., 2005; Song et al., 2005). It has been confirmed that SARS-CoV-2 also uses the ACE2 receptor (Letko & Munster, 2020; Zhou et al., 2020). However, it is important to remember that successful adaptation to a new host requires not only these mutations regarding receptor binding, but a whole series of successful mutations in genes that optimize virus replication and transmission in the new host (Holmes, 2005).

Origins

- It has been hypothesised that all mammalian coronaviruses were derived from ancestral viruses infecting bats (Balboni et al., 2012), though some may have more recently come from rodents (Cui et al., 2019) (see Figure 2). SARS-CoV is thought to have emerged as a variant of a coronavirus infecting Horseshoe bats in Asia (Wang & Eaton, 2007). Since the SARS-CoV outbreak, a large number of SARSr-CoV viruses have been discovered in their natural reservoir host, bats (Zhou et al., 2020).
- Other coronaviruses that have made species jumps have generally lost their capacity to infect animals in which they were originally found (Müller et al., 2012). Coronaviruses are highly diverse as a result of the infidelity of RNA-dependent RNA polymerase, high frequency of homologous RNA recombination, and their large genomes. Among all hosts, the diversity of coronaviruses is most marked in bats and birds, which may be a result of their species diversity, ability to fly, environmental pressures, and habits of roosting and flocking. It is thought that bat viruses comprise the natural reservoir of genetic diversity of alpha and beta coronaviruses, and bird viruses are the natural reservoir of genetic diversity for gamma and delta coronaviruses. Increased identification of closely-related viruses in different species supports the idea that coronaviruses have frequently been capable of making species jumps in the past (Woo et al., 2009).
- Over the past 30 years, several coronavirus cross-species transmission events, as well as changes in virus tropism, have given rise to significant new animal and human diseases including: bovine coronavirus (BCoV), human coronaviruses OC43 and 229E, canine coronavirus (CCoV), feline coronavirus (FCoV), and several coronaviruses in pigs (e.g., porcine respiratory coronavirus, PEDv, TGEV and SARS-CoV) (Aleksiev et al., 2008; Le Poder, 2011; Lorusso et al., 2008; Perlman & Netland, 2009; Vijgen et al., 2005; Zhou et al., 2018). Betacoronaviruses are particularly known to cross between species (Boileau & Kapil, 2010). Relatively few animal coronavirus strains have been fully sequenced for comparative phylogenetic analysis to trace their evolutionary origins (Saif, 2004).
- Zoonotic bat-transmitted viruses frequently have to be amplified via domesticated animals to pose a significant risk to humans (e.g. Hendra and Nipah viruses). Some hypotheses suggest that SARS-CoV palm civets (wild cat-like carnivores) acted as amplifying hosts for SARS-CoV before it was transmitted to humans (Field, 2009; Hon et al., 2008; Wang & Eaton, 2007), while others

suggest that it went directly from bats to humans, and then from humans to civets and pigs (and, in rare cases late in the outbreak, back to humans) (Ohio State University, 2008).

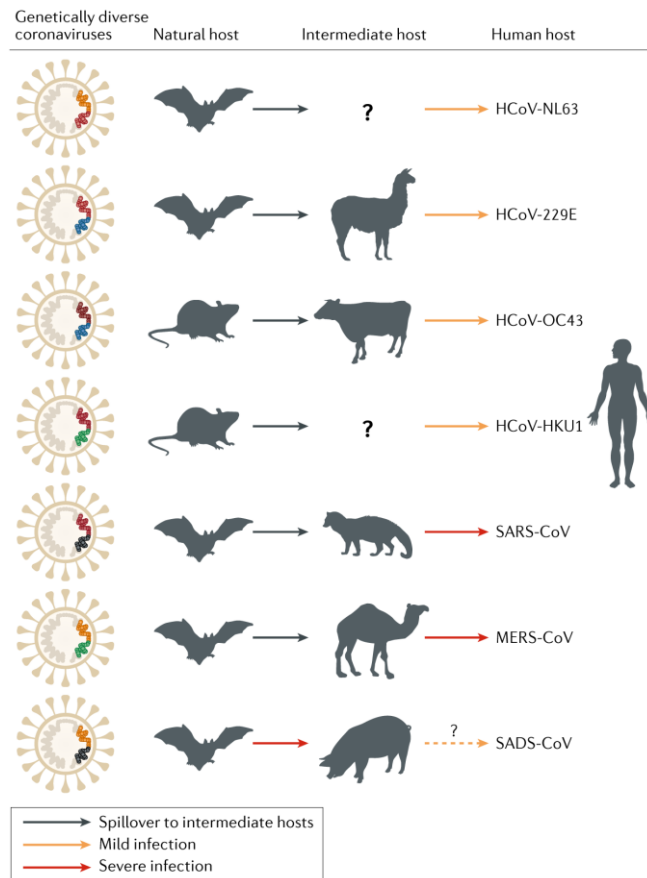


Figure 2: Animal origins of human coronaviruses (Cui et al., 2019).

- The origin of SARS-CoV-2 is still being investigated. However, it is likely to have recently involved bats, which is supported by the close phylogenetic relationship to bat coronaviruses (Zhou et al., 2020). Involvement of another species cannot be discounted (Robertson, 2020). All current evidence points to wild animals sold illegally in the Huanan Seafood Wholesale Market as the initial source (Wenjie et al., 2020). Several speculations have been made to date on a potential intermediary host including: snakes (Ji et al., 2020), bamboo rats, crickets (ProMED-Mail, 2020), fish (Ramaiah & Arumugaswami, 2020), and pangolins (Cyranoski, 2020). These have primarily been based on preliminary genetic information, which should be interpreted with caution. A mammalian source is most likely. Further epidemiological and laboratory investigations are required to confirm any potential amplifying and/or reservoir hosts. Given the tight clustering of the SARS-CoV-2 isolates in phylogenetic trees, it seems most likely that a single and recent spillover event from animals to humans has occurred (Bedford et al., 2020; Robertson, 2020; Zhou et al., 2020).

- Regardless of the potential animal origins of SARS-CoV-2, the predominant route of subsequent transmission appears to be from human to human (Chan et al., 2020; World Organisation for Animal Health, 2020).

Infections in Animals

- Coronaviruses in general infect a wide range of birds and mammals (Saif, 2004). Human coronaviruses cause up to one-third of upper respiratory tract infections in adults (PHAC unpublished information). Very little is known about coronaviruses circulating in wildlife (Saif, 2004).
- Some coronavirus strains are zoonotic, while others are not. MERS-CoV, for example, is a zoonotic coronavirus with ongoing transmission from dromedary camels to humans (World Organisation for Animal Health, 2020).
- Information on related coronaviruses:

SARS-CoV

- **Non-human primates and rodents:** Animal models include non-human primates and rodents (Gretebeck & Subbarao, 2015). Evidence of infection in wild rodents was also detected during outbreak investigations (Ng, 2003; Wang et al., 2005).
- **Ferrets:** In experimental infections, 3 out of 6 ferrets became lethargic within 2-4 days post-infection, and one of these died at day 4. These animals transmitted the virus to uninfected animals housed with them (Martina et al., 2003).
- **Cats:** In the same experiments, all six inoculated domestic cats were sub-clinically infected, and they were also able to transmit infection to uninfected animals (Martina et al., 2003). During outbreak investigations of an apartment block in Hong Kong with more than 300 infected residents, viral remnants were found in throat or rectal swabs from five domestic cats, and antibodies were detected in one of them (Ng, 2003). Chen et al. (2005) found no antibodies or virus in 11 cats sampled in China. A survey conducted at a Chinese market in 2004 before the mass culling of palm civets found four cats positive by RT-PCR. However, since the environment was heavily contaminated at that time, it is not known whether these animals were actually susceptible hosts or only mechanical vectors. Samples were taken from 13 cats after culling and disinfection with negative results (Wang et al., 2005).
- **Dogs:** The outbreak investigation in Hong Kong also identified viral remnants in throat or rectal swabs from one dog (Ng, 2003). Chen et al. (2005) found no antibodies or virus in 20 dogs sample in China.
- **Pigs and other livestock:** In 2003, surveillance for SARS-CoV in animals was conducted in China. Antibodies were detected in 2/108 pigs, and virus was then isolated from one of them. No clinical signs were reported. Sequence and epidemiology analyses suggested that the pig was infected by a virus of human origin. It was proposed that this might have been transmitted by the feeding of garbage from restaurants. No antibodies or virus were detected in the other animals tested, including: cattle (n=60), chickens (n=11), and ducks (n=30) (Chen et al., 2005). The CFIA National Centre for Foreign

Animal Disease inoculated chickens and pigs with SARS-CoV by multiple routes. Viral RNA was detected in both species, but no virus was isolated. Antibodies were detected in pigs. No clinical signs or gross pathological changes were evident. Although susceptible to asymptomatic infection, pigs are unlikely to act as amplifying hosts (Weingartl et al., 2004).

- **Other wild animals:** During the SARS-CoV outbreak investigations in China, the virus was isolated from palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*), and antibodies were detected in Chinese ferret badgers (*Melogale moschata*) (Guan et al., 2003). The survey conducted at the Chinese market in 2004 before the mass culling of palm civets found three red foxes and a wild boar positive by RT-PCR. As mentioned for cats, it is not known whether these animals were actually susceptible hosts or only mechanical vectors (Wang et al., 2005).

MERS-CoV

- **Bats:** MERS-CoV may also have originated in bats, but it appears to not be currently circulating at a high rate in bat populations (Memish et al., 2013).
- **Dromedary camels (*Camelus dromedarius*):** This species has been confirmed by several studies to be the natural host and zoonotic source of the MERS-CoV infection in humans. It has been associated with mild upper respiratory signs in some dromedary camels (World Organisation for Animal Health, 2019).
- **Livestock and horses:** Limited serological testing of domestic livestock in Saudi Arabia detected no antibodies to MERS-CoV in sheep (n= 100), goats (n= 45), cattle (n= 50) and chickens (n= 240). Antibody to bovine coronavirus (BcoV) was common in cattle tested from this region, but these sera did not cross-react with MERS-CoV (Perera et al., 2013). Sera from animals (Cattle (n=80), sheep (n=40), goats (n=40)) in the Middle East (Oman) and from elsewhere (Spain, Netherlands, Chile) were tested for MERS-CoV. No antibodies were detected (Reusken et al., 2013). Horse serum from UAE (n=192) and Spain (n=861) was tested for MERS-CoV. None of the tested serum samples showed reactivity, suggesting that no previous exposure of equids to MERS-CoV has occurred in the United Arab Emirates and Spain (Meyer et al., 2015). Sera from water buffaloes (n=8), cows (n=25), sheep (n=5) and goats (n=13) collected in Egypt were all negative for MERS-CoV antibodies (Perera et al., 2016).
- Other species may be susceptible to infection with MERS-CoV. However, their epidemiological significance has not been proven (World Organisation for Animal Health, 2019).

Distribution

- As a category, human and animal coronaviruses are globally distributed.
- Betacoronaviruses of bats have not been found in North America to date, however our understanding of the geographic distribution of wild animal coronaviruses must be considered rudimentary at present. An alphacoronavirus has been isolated from a bat in Canada (Misra et al., 2009).

- The distribution of SARS-CoV-2 in animals is unknown.

Transmission

- Some coronaviruses are transmitted primarily among humans, others among animals, but zoonotic transmission (from animals to humans) has been shown to occur periodically with MERS-CoV (World Organisation for Animal Health, 2020).
- Human coronaviruses are transmitted person-to-person through direct contact with secretions or through fomites and via respiratory droplets (Public Health Agency of Canada, 2010; 2019).
- Human coronavirus infection is usually restricted to the respiratory tract, but SARS-CoV can probably be spread by the faecal-oral route as well as by the respiratory droplet/aerosol route (Hong Kong Department of Health, 2003; Lapinsky & Granton, 2004), and stool was found to be a useful type of specimen for diagnosis of SARS-CoV infection.
- This versatility in mode of transmission is something that is likely to be true of other domestic animal and wildlife-related coronaviruses that could cross into humans, as many animal-specific coronaviruses are enteric or pneumo-enteric in nature, and are shed in feces (e.g. BCoV, PEDv, TGEV, FCoV, CCoV) (Lau et al., 2005; Saif, 2004; Shi & Hu, 2008; Su et al., 2016).

Environmental Survival

- Although studies suggest that under the right conditions, coronaviruses could survive on surfaces in health care environments for days (e.g., 5-28 days, depending on relative humidity) (Casanova et al., 2010), experience with SARS-CoV and MERS-CoV suggests that these viruses spread primarily by large respiratory droplets, rather than by aerosols and fomites (Perlman, 2020). The US CDC states that there is likely very low risk of spread from products or packaging that are shipped over a period of days or weeks at ambient temperatures (Centers for Disease Control and Prevention, 2020).
- Environmental cleaning products registered in Canada with a Drug Identification Number (DIN) and labelled as a broad-spectrum virucide are effective against SARS-CoV-2 (Public Health Agency of Canada, 2020). This would be similar to SARS-CoV, which is disinfected by household bleach (5 minutes), ice-cold acetone (90 seconds), ice-cold acetone/methanol mixture (40:60, 10 minutes), 70% ethanol (10 minutes), 100% ethanol (5 minutes), paraformaldehyde (2 minutes), and glutaraldehyde (2 minutes). Commonly used brands of hand disinfectants also inactivate SARS-CoV (30 seconds). SARS-CoV is sensitive to heat (60°C for 30 minutes), and UV radiation (60 minutes) (Public Health Agency of Canada, 2019).

Vaccines

- No vaccines are currently available for SARS-CoV-2, and there are no licensed vaccines for SARS-CoV or MERS-CoV.
- Bovines: licensed vaccines (modified live and killed) are available in Canada against diseases caused by enteric bovine coronavirus strains. Currently, there are no vaccines against respiratory disease caused by bovine respiratory coronavirus strains. Usually, enteric coronavirus vaccines don't provide protection against the respiratory disease caused by pneumotropic bovine coronavirus strains.



INFO SHEET: CORONAVIRUSES AT THE HUMAN-ANIMAL INTERFACE

- Canine: licensed vaccines are available in Canada for enteric canine coronavirus. The American Animal Hospital Association (AAHA) does not recommend vaccination of dogs with the enteric coronavirus vaccines because disease in dogs is not severe and is usually self limiting. There are currently no vaccines against canine respiratory coronaviruses. The enteric canine coronavirus vaccines are unlikely to protect against the respiratory disease caused by canine coronavirus.
- Porcine: there are no licensed porcine coronavirus vaccines available in Canada. There are two conditionally licensed PEDV vaccines available in USA, which are imported only under emergency situations to control PEDV outbreaks in Canada. There are a couple of modified live TGEV vaccines licensed in the USA.
- Avian: licensed vaccines are available in Canada against avian infectious bronchitis virus (a *Gammacoronavirus*) which causes infectious bronchitis.
- Others: Currently, there are no licensed coronavirus vaccines against other livestock species.
- It is unlikely that these vaccines, or vaccines for more distantly-related animal coronaviruses, would provide any cross-protection against SARS-CoV-2.

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