

Review on transmission of SARS-CoV-2 at the human-animal interface

Project for reviewing risks of SARS-CoV-2 infection between animals and humans

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Dog

Dogs can be infected with SARS-CoV-2, and human-to-dog transmission has been confirmed.

Dogs can acquire infection in households from SARS-CoV-2-infected humans (Sit et al., 2020). In addition, the virus can infect culture cells expressing canine ACE2 in the laboratory (Zhang et al., 2021). However, in the natural environment, transmission from human to dogs is quite rare (Temmam et al., 2020). The suggested reasons for this are that SARS-CoV-2 replicates poorly in dogs (Shi et al., 2020) and that the binding affinity of receptor binding domain of SARS-CoV-2 to canine ACE2 is lower than that of human ACE2 (Zhang et al., 2021). Clinically, The oral and nasal swabs from dogs tested positive for SARS-CoV-2 without symptoms (Sit et al., 2020), and the viral sequences from dogs were identical to SARS-CoV-2 across the full genome (Temmam et al., 2020). However, there were no obvious changes in clinical condition (Sit et al., 2020) and no antibodies against SARS-CoV-2 were detectable in their blood one month after the case was reported (Temmam et al., 2020).



Cat

Cats can get infected with SARS-CoV-2 and were one of the first animals to be diagnosed with SARS-CoV-2 infection.

Natural cases of infection in cats have been found in several countries. Both human-to-cat and cat-to-cat infections have been confirmed (Vanessa R B. et al., 2020). The symptoms shown in cats were identical to those in humans and the specific antibodies for SARS-CoV-2 were detected in cats (Corinne S. et al., 2020). However, the replication of the virus in cat-derived cell lines was not efficient compared with human cell lines (Wang L. et al., 2021). Furthermore, SARS-CoV was detected in cats (Martina et al., 2003) and cats have been used as an animal model for SARS-CoV (Van Den Brand et al., 2008).



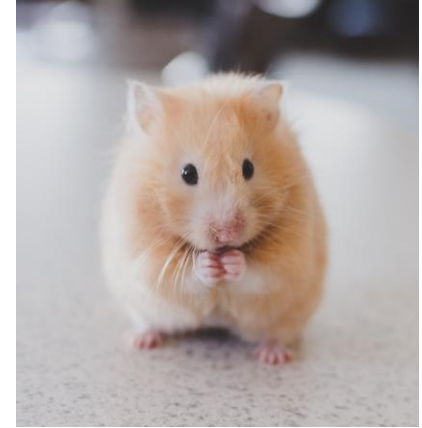
Zoo animals (Tiger & Lion)

Tigers and lions were infected with SARS-CoV-2 and the possibility of transmission from these animals to human was suggested.

These animals showed clinical respiratory signs such as an intermittent cough or audible wheezing. Live SARS-CoV-2 and viral RNA were detected in the respiratory tract and feces from these animals. Comparative analysis of the viral genome to human-isolated virus support the possibility of transmission from an infected human to the animals (McAlouse et al., 2020).

Hamster

Golden hamsters are susceptible to SARS-CoV-2 infection.



The virus replicated in the lung with pneumonia (Imai et al., 2021). SARS-CoV-2 was transmitted efficiently from inoculated golden hamsters to naive hamsters by direct contact and via aerosols (Sia et al., 2020). Amino acid sequence and in vitro experiments showed the possibility of the binding of hamster's ACE2 and SARS-CoV-2 (Damas et al., 2020). Thus, the golden hamster is a well-established small animal model for the study of SARS-CoV-2 infection.



Rabbit

Rabbits are susceptible to SARS-CoV-2.

An experimental study showed that rabbits can be infected with the virus in the upper respiratory tract and can shed infectious agents into the environment (Mykytyn AZ et al., 2021). In amino acid sequence analysis, there was high similarity between rabbit and human ACE2 (Damas J et al., 2020). The rabbit ACE2 bound to the virus, which supported proliferation and entry of the virus (Zhao et al., 2020). In other coronavirus infections, MERS-CoV was detected in rabbit without significant histopathologic changes and symptoms (Haagmans et al., 2015). We could not find a study about natural infection of SARS-CoV-2.

Ferret

Ferrets are susceptible to SARS-CoV-2 infection.



ACE2 expression in ferrets was observed in the upper respiratory tracts but not lower tracts (Lean et al., 2021). Inoculation of SARS-CoV-2 into ferrets induced fever and loss of appetite and the viral RNA and infectious virus were detected from nasal washes (Shi J et al., 2020). Furthermore, the Chinese ferret-badger has been reported to be susceptible to SARS-CoV (Gautam et al., 2020).

Cattle

No infectious SARS-CoV-2 was detected from experimentally inoculated cattle.



Phylogenetic and structural analysis of ACE2 and SARS-CoV-2 spike protein demonstrated that ACE2 protein of cattle is one of the most permissive to SARS-CoV-2 (Qiu et al., 2020). In addition, direct binding of cattle ACE2 and SARS-CoV-2 spike protein was experimentally confirmed (Conceicao et al., 2020). However, experimentally SARS-CoV-2-inoculated cattle showed very limited viral replication and viral neutralizing antibodies and no cattle-to-cattle transmission of SARS-CoV-2 was observed (Lorenz et al., 2020 and Shollie et al., 2021).



Horse

Horses possibly have the potential to be infected with SARS-CoV-2.

Sequence identities of horse ACE2 and susceptibility score that predicts the risk of SARS-CoV-2 infection showed that horses have high potential to get infected with SARS-CoV-2 (Alexander et al., 2020). In vivo experiment and serosurveillance are required for further evaluation of SARS-CoV-2 susceptibility of horses.

Pig

Pig is likely not a potential source for SARS-CoV and SARS-CoV-2.



Experimentally SARS-CoV-2-inoculated pigs showed no viral replication, seroconversion, or pig-to-pig transmission (Kore Schlottau. et al., 2020). In another experiment, SARS-CoV-2-inoculated pigs also showed no viral replication, but pigs inoculated with SARS-CoV-2 intramuscularly or intravenously showed seroconversion (Vergara-Alert J et al., 2020).



Poultry

(chickens, turkeys, ducks, quail, geese, etc.)

In experimental settings, no poultry was confirmed to be susceptible to SARS-CoV-2.

All the results demonstrated that poultry are unlikely to serve as a role in the maintenance or transmission of SARS-CoV-2 (Schlottau et al., 2020).



Alpaca

Alpaca possibly have susceptibility to SARS-CoV-2.

A novel coronavirus associated with an acute respiratory disease in alpacas (Alpaca Coronavirus, ACoV) was genetically most similar to the common human coronavirus (HCoV) 229E with 92.2% nucleotide identity over the entire genome (Crossley B M et al., 2012). Experimentally MERS-CoV-inoculated alpaca showed viral replication without clear clinical symptoms (Crameri G et al., 2016). In addition, MERS-CoV receptor DPP4 was shown as a candidate binding target of the SARS-CoV-2 spike protein (Li Y et al. 2020). These data suggest that alpaca possibly have susceptibility to SARS-CoV-2, although in vivo experiments are required for further evaluation.

Mink

SARS-CoV-2 was detected in farmed mink with symptoms of respiratory disease, and the source of mink infection was mink farm workers.



SARS-CoV-2 infection in farmed mink was first reported in Netherland and some of infected minks showed severe respiratory symptom such as interstitial pneumonia (Nadia Oreshkova et al., 2020). Whole genome sequence and intensive epidemiological analysis demonstrated that both human-to-mink and mink-to-human transmission of SARS-CoV-2 were occurred within mink farms (Oude Munnink BB et al., 2021). Binding region of ACE2 of mink and human were both highly conserved, suggesting SARS-CoV-2 infection between mink and human (Oude Munnink BB et al., 2021).



Bat

Bats, especially fruit bats, are one of the high-risk species to transmit SARS-CoV-2.

Bats are known to be natural hosts of several coronaviruses including SARS-CoV-2-related coronaviruses (Wacharapluesadee et al., 2021), such as bat CoV RaTG13, which shares the highest sequence homology with SARS-CoV-2 among known coronaviruses (Zhou et al., 2020). In an experimental infection of SARS-CoV-2 to Egyptian fruit bats (*Rousettus aegyptiacus*), infected bats did not show clinical signs or mortality, while bat-to-bat transmission was confirmed (Schlottau et al., 2020). MERS-CoV can also infect Jamaican fruit bats (*Artibeus jamaicensis*) without any clinical signs (Munster et al., 2016). Thus, bats are ones of the highest-risk species to transmit SARS-CoV-2. Furthermore, coronavirus circulation in bats should be monitored to prepare for a future emergence of novel coronaviruses.

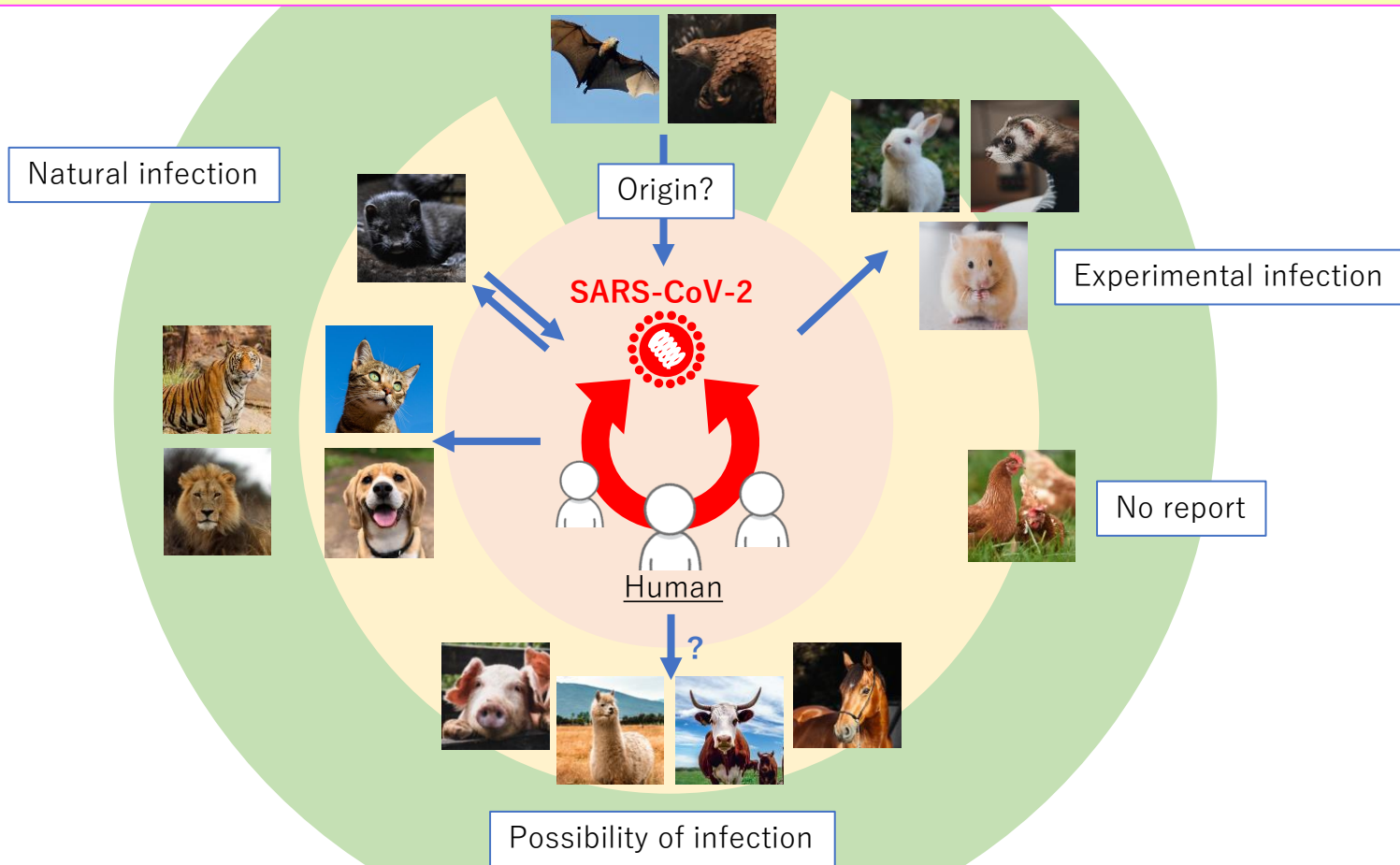


Pangolin

Pangolin is one of the high-risk species to transmit SARS-CoV-2.

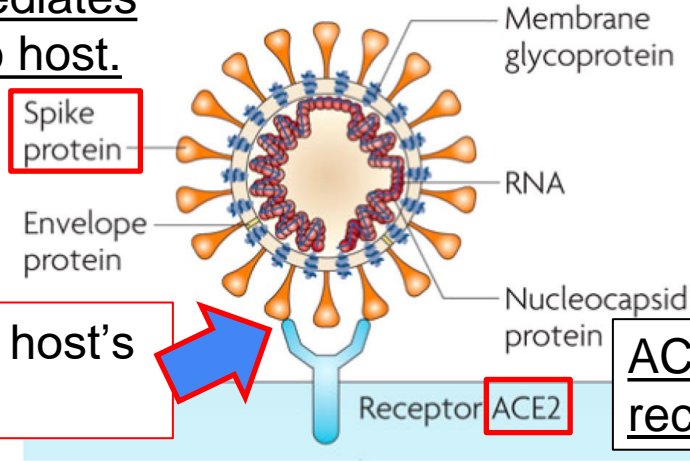
Pangolin-CoV is the second closest relative to SARS-CoV-2 after the bat CoV RaTG13 (Zhang et al., 2020). Pangolin-CoV possesses ACE2 binding motif of SARS-CoV-2, which is not in bat CoV RaTG13 (Lam et al., 2020). SARS-CoV-2 S protein-binding sites on pangolin ACE2 molecule are similar to those of human ACE2 (Wei et al., 2021), and pangolin ACE2 strongly binds to SARS-CoV-2 S protein to efficiently support the virus entry (Zhao et al., 2020). Thus, pangolin is one of the high-risk species to transmit SARS-CoV-2 and also will be a possible host in the future emergence of new coronaviruses.

Human-animal relationship in SARS-CoV-2 infection



The host receptor of SARS-CoV-2: Angiotensin I converting enzyme 2 (ACE2)

A surface spike (S) protein mediates viral recognition and entry into host.



The affinity determines the host's susceptibility to infection.

ACE2 is functional receptor for S protein.

Du L, *et al.* Nat. Rev. Microbiol., 2009

ACE2 is expressed in most vertebrates, but the amino acid sequences differs with species.



Receptor recognition is an important factor determining host range