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Besvarelse vedr.

- Veterinær betydning af Coronavirus disease 2019 (COVID-19) hos mennesker

Baggrund/kontekst for bestilling (hvorfor, til brug for hvad)

- COVID-19 skyldes en helt ny type coronavirus (SARS-CoV-2). Danmark forbereder sig på en potentiel epidemi blandt mennesker. Fødevarestyrelsen modtager allerede flere forespørgsler om COVID-19 sygdommen i relation til forskellige former for hold af dyr. Der er derfor brug for konkret viden om SARS-CoV-2 virussets veterinære potentiale. Der kan tages udgangspunkt i et scenarie, hvor COVID-19-smittede personer er i hjemme-karantæne, hvor der kan være kontakt til dyr.

Svar

Veterinary importance of Coronavirus disease 2019 (COVID-19) in humans

Background

There is currently much global attention on the human cases of COVID-19, and the coronavirus, termed severe respiratory syndrome coronavirus-2 (SARS-CoV-2), which is responsible for the infection. It is highly likely that this virus has spread from horseshoe bats (*Rhinolophus spp.*) to humans, possibly via intermediate hosts but no such intermediate host has so far been definitively identified. This would mirror the spread of the SARS-CoV to humans from these bats, probably via civet cats, that occurred in 2002 in the Guangdong province of China.

Many different coronaviruses are known; they are classified into 4 distinct genera, α (alpha), β (beta), γ (gamma) and δ (delta). These viruses can infect a wide range of different hosts including mammals and birds but each individual virus seems to have a narrow host range. Bats appear to be the wildlife reservoir for many different alpha- and betacoronaviruses. However, similar coronaviruses have also been identified in many other mammalian species, e.g. pigs, cattle, horses, dogs, cats, mink, ferrets, rats and mice. The gamma- and deltacoronaviruses have predominantly been identified in birds but a porcine deltacoronavirus was also detected recently.

Coronaviruses can cause respiratory and enteric infections. Until the appearance of SARS in 2002, these viruses were not considered major problems for human health, since the known human coronaviruses usually produced only mild respiratory disease. However, since 2002, three betacoronaviruses, namely SARS-CoV, MERS-CoV and SARS-CoV-2, have all emerged and caused severe respiratory diseases in humans.

In animals, porcine epidemic diarrhea virus (PEDV), an alphacoronavirus, was first identified in Europe in 1978. This virus causes enteric disease that is characterised by diarrhoea and vomiting leading to severe dehydration with high mortality among young piglets and hence severe economic losses. During the 1980's and 1990's, the virus spread within Europe and also in Asia where it caused significant problems. After this time, however, the disease declined within Europe but a new wave of PEDV infections occurred from 2010 onwards in China and adjacent countries, and the virus spread, for the first time, into the USA in 2013. About 7 million piglets died in the course of one year in the USA, and it affected many different states within the country (see Jung & Saif, 2015).

Host of origin for SARS-CoV-2 and presence in Denmark

The origin of pathogenic coronaviruses has recently been reviewed (Cui et al., 2019) and a recent report has addressed the origin of the SARS-CoV-2 (Andersen et al., 2020).

The SARS-CoV-2 is most closely (96% sequence identity) related to a SARS-related coronavirus, termed RaTG13, isolated from a *Rhinolophus affinis* bat. Other SARS-CoV-2 related viruses have been detected in Malayan pangolins. It appears that key amino acid residues, within the receptor binding domain (RBD), located in the spike (S) protein of the SARS-CoV-2, which are important for binding to the cellular receptor (ACE2), are different between this virus and its closest relative; this suggests some adaptation to its new host (humans). The ACE2 receptor is present in other mammalian species, including pigs, cats and ferrets. Furthermore, the S protein of SARS-CoV-2 has also acquired a polybasic stretch of amino acid residues. The functional consequences of this latter change are not yet established but it could modify the glycosylation of the S protein that is exposed on the surface of the virus particle. These two changes in the virus, compared to its closest known relative, could have occurred within a human host or within an unknown intermediate host (possibly one change occurred in one host and then the second change in humans). Currently, there is no known host animal that has a virus that is (nearly) identical to the human SARS-CoV-2 (note, for a coronavirus, with a genome of about 28,000 nucleotides (nt), even a 1% difference in its sequence corresponds to about 280 nt changes thus the 96% identity between the SARS-CoV-2 and its closest relative (in horseshoe bats) represents over 1000 nt differences).

Presence/detection of SARS-CoV-2 in other animal species

Since the SARS-CoV has been known for a much longer period of time than the SARS-CoV-2, there is much more information about the origin of the SARS-CoV. Many different, SARS-related

coronaviruses (SARSr-CoVs) have been identified from bats but the strains from the horseshoe bats are most closely related to the SARS-CoV. Horseshoe bats are found in many countries in Asia and in Europe (but not in Denmark). No direct progenitor of the SARS-CoV has been identified but it seems that recombination between SARSr-CoVs in these bats gave rise to the direct progenitor of the SARS-CoV, which was likely transmitted to civet cats where it acquired additional changes prior to its transmission to humans.

There are some reports that the SARS-CoV can infect additional animal species. After the outbreak of SARS in Guandong, China, a range of domestic and wild animals were examined for the presence of the SARS-CoV. Virus and RT-PCR positive cases were found in the Himalayan palm civet and in a raccoon dog. Furthermore, a seropositive Chinese ferret badger was also identified (Guan et al., 2003). However, in the same study, four domestic cats were tested for antibodies and virus and there was no evidence for infection. In addition, as a result of serosurveillance, in the vicinity of a SARS outbreak in Tianjin, China, two pigs, out of 242 screened, were found seropositive for anti-SARS-CoV antibodies. One of these pigs also proved to be RT-PCR positive and the virus was isolated from it (Chen et al., 2005). However, it is apparent that no spread of the virus within these pigs had occurred and no disease was apparent. Under experimental conditions, intratracheal inoculation of domestic cats and ferrets with the SARS-CoV resulted in infection in these animals, with virus shedding from 2 days until 10 or 14 days post inoculation, respectively. No clinical signs were seen in domestic cats but the ferrets became lethargic from 2-4 days post inoculation. Transmission to co-housed cats and ferrets was also observed (Martina et al., 2003). It is also noteworthy, that another coronavirus derived from horseshoe bats, in the Guandong province of China, caused an outbreak of severe acute diarrhea syndrome (termed SADS) in pigs.

This outbreak resulted in the death of about 25,000 pigs. The virus responsible for this outbreak in 2016 was a novel alphacoronavirus, whereas the SARS-CoV and SARS-CoV-2 are betacoronaviruses.

There has been a report of a RT-PCR positive tests for SARS-CoV-2 in nasal and oral swab samples collected from a dog in Hong Kong kept in quarantine after hospitalization of its owner due to COVID-19. The dog, which showed no clinical signs, was tested positive on three separate occasions, each 48 hours apart. It appeared initially that this may have reflected environmental contamination from the owner but there is a need for further testing to determine if this dog became infected or not.

It is apparent that coronaviruses are usually quite host specific but occasionally jumps to other hosts can occur. This seems to require significant genetic change, e.g. through recombination. It cannot be predicted whether the species jump that has already occurred for the SARS-CoV-2 will facilitate the spread of the virus into other animal species but this does not seem to have been the case for the SARS-CoV. Interestingly, the MERS-CoV, seems to have been present in dromedary camels for many years before the first cases of disease in humans were recognized. The MERS-CoV is also closely related to certain bat coronaviruses within the betacoronaviruses (lineage C), although none of these viruses appear to be the direct progenitor of the MERS-CoV and it seems that recombination events have occurred to generate this zoonotic virus. Thus, it seems that the production of coronaviruses with a new host range occurs as a result of recombination events between different coronaviruses. Such events may be relatively common among this family of viruses but it may be rather rare for this process to generate a novel virus with an extended host range.

Conclusions

- The original host of SARS-CoV-2 is not known. The closest known relatives are found in horseshoe bats (*Rhinolophus spp.*). Other SARS-CoV-2 related viruses have been detected in Malayan pangolins
- No horseshoe bats are found naturally in Denmark but they are present in Europe
- SARS-CoV-2 has been detected in one dog in Hong Kong owned by a COVID-19 patient. It is not yet known if the dog was infected or just contaminated. So far SARS-CoV-2 has not been detected in any other animal hosts
- Different coronaviruses are known to be host species specific. To jump from one species to another seems to require multiple nucleotide (genetic) changes, e.g. by recombination
- Experimental infection and transmission of SARS-CoV to ferrets and domestic cats has been demonstrated but it is not known if transmission to these animals can occur under natural conditions
- Based on the general information on coronaviruses and on SARS-CoV, and on the limited knowledge on SARS-CoV-2, jumps to other species seem not very likely but cannot be excluded
- If/when a jump to a new host occurs further sustainable spread within the new host population likely requires further adaptation of the virus to the new host
- Establishment of a reservoir for SARS-CoV-2 in domestic animals or in wildlife in Denmark seems unlikely based on the current limited knowledge

References:

Anderson KG et al., see: <http://virological.org/t/the-proximal-origin-of-sars-cov-2/398>

Chen W, Yan M, Yang L, et al. SARS-associated coronavirus transmitted from human to pig. *Emerg Infect Dis*. 2005;11(3):446–448. doi:10.3201/eid1103.040824

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17(3):181–192. doi:10.1038/s41579-018-0118-9

Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*. 2003;302(5643):276–278. doi:10.1126/science.1087139

Jung K, Saif LJ. Porcine epidemic diarrhea virus infection: etiology, epidemiology, pathogenesis and immunoprophylaxis. 2015; *Vet. J*. 204: 134–143. pmid:25841898

Martina BE, Haagmans BL, Kuiken T, et al. Virology: SARS virus infection of cats and ferrets. *Nature*. 2003;425(6961):915. doi:10.1038/425915a
