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Besvarelse vedr.

Vurdering af smitterisiko for COVID-19 hos kaniner

Bestilling

Fødevarestyrelsen ønsker DK-VET's vurdering af nedenstående spørgsmål angående smitterisiko for COVID-19.

Kan kaniner smittes med COVID-19, og hvor sandsynligt er det? Kan kaniner udskille smitte og dermed smitte andre dyr af samme eller af en anden art?

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

Af et nyt hollandsk studie fremgår, at kaniner er en modtagelig art for COVID-19, men det fremgår ikke klart, om kaniner kan videregive smitten.
Se https://www.biorxiv.org/content/10.1101/2020.09.01.277152v1.full.pdf

Det forlyder, at eksperimentelle studier pågår hos FLI med henblik på at undersøge SARS-Co 2 infektion af kaniner. Fødevarestyrelsen har ikke nærmere oplysninger om dette.

DK-VET kan evt. søge yderligere oplysninger om ovenstående studier.

Fødevarestyrelsen udtager af prøver fra kaniner på en COVID-19 smittet minkfarm i de nærmeste dage.

Evt. bemærkninger (historik, relaterede bestillinger osv.)

Udklip fra oven for omtalte hollandske publikation:

Experimental infections in dogs (*10*), cats (*10*, *11*), ferrets (*10*, *12*), hamsters (*13*, *14*), rhesus macaques (*15*), tree shrew (*16*), cynomolgus macaques (*17*), grivets (*18*), common marmosets (*19*), rabbits (*20*), and fruit bats (*21*) have shown that these species are susceptible to SARS-CoV-2, and experimentally infected cats, tree shrews, hamsters and ferrets could transmit the virus. In contrast, experimental infection of pigs and several poultry species with SARS-CoV-2 proved to be unsuccessful (*10*, *21*, *22*). SARS-CoV-2 has also sporadically been identified in naturally infected animals. In the USA and in Hong Kong, SARS-CoV-2 RNA has been detected in dogs (*23*). In the Netherlands, France, Hong Kong, Belgium and the USA, cats

Referencen:

20. B. L. Haagmans, D. Noack, N. M. Okba, W. Li, C. Wang, R. de Vries, S. Herfst, D. de Meulder, P. van Run, B. Rijnders, C. Rokx, F. van Kuppeveld, F. Grosveld, C. GeurtsvanKessel, M. Koopmans, B. Jan Bosch, T. Kuiken, B. Rockx, *bioRxiv*, in press, doi:10.1101/2020.08.24.264630.

Svar

‣The pre-print (which means a not peer-reviewed manuscript and so not yet accepted for publication in a scientific journal) from Munnink et al., cites a reference (20) for evidence of experimental infection of rabbits by SARS-CoV-2. The reference 20 is another unpublished pre-print, this is from Haagmans et al. This manuscript is entirely concerned with the protection of Syrian hamsters against SARS-CoV-2 infection using human antibodies, it does not have information about infection of rabbits. Thus, there appears to be an error in the pre-print from Munnink et al.
However, we have now identified another pre-print (Mykytyn et al., (also from the Haagmans lab)) which is entitled “Susceptibility of rabbits to SARS-CoV-2” and this is now discussed below.
To provide some background, we briefly review related studies on assessing the susceptibility of other animal species to SARS-CoV-2 and then describe the new studies in rabbits from Mykytyn et al.

There have been a variety of studies examining the sensitivity of a variety of species to infection by SARS-CoV-2. Clearly, the American mink as well as humans are susceptible to infection by the virus. In the majority of cases, the infection is mild and serious disease mainly occurs in humans when other co-morbidities are present (e.g. obesity, diabetes etc.).

Evidence for infection of cats (Halfmann et al., 2020) and dogs (Sit et al., 2020) from infected humans and also on farms with infected mink (Oreshkova et al., 2020; Hammer et al., submitted) has also been reported. Experimental studies with cats and dogs have also confirmed the susceptibility of these species to the virus following inoculation (Shi et al., 2020). In addition, ferrets, certain non-human primates (macaques), Syrian hamsters and transgenic mice that

express the human ACE2 receptor have been found to be susceptible to infection by SARS-CoV-2 albeit with inapparent or mild disease (see review by Heegaard et al., in press). Non-transgenic mice, chickens and pigs do not appear susceptible to the virus. Clearly, there are many different species that have not been tested.

An extensive analysis of the relationship between the cellular receptor for SARS-CoV-2, termed ACE2, from different animal species has been performed to try to predict the susceptibility of different hosts to infection. For example, Damas et al (2020) predicted the host range of SARS-CoV-2 from analysis of the ACE2 sequences. As may be expected, non-human primates were predicted to be highly efficient at binding the SARS-CoV-2 Spike protein while cats, cattle, goats, sheep and rabbit were only predicted to bind the SARS-CoV-2 with medium efficiency. Dogs, horses and pigs were predicted to have low ability to bind the virus while mice and the American mink (*Neovison vison*) were predicted to be very poor in binding the SARS-CoV-2, which indicates a limitation of this approach since clearly these mink can be infected very efficiently.

The ACE2 proteins from humans, bats, pigs and civets were able to confer virus susceptibility to human HeLa cells, in cell culture, but the mouse ACE2 did not (Zhou et al., 2020). However, it is clear that this assay also has limitations since two separate studies have failed to demonstrate infection of pigs by the virus (Schlottau et al., 2020; Shi et al., 2020). Infection requires multiple interactions between the virus and the host, not only at the level of the virus binding to the cellular receptor.

The new pre-print from Mykytyn et al. is the first study that we are aware of concerning the susceptibility of rabbits. There are two parts to the study. The rabbit ACE2 protein was expressed in a receptor-deficient cell line and it was found that the rabbit ACE2 protein was able to support entry of the SARS-CoV-2 virus into the cells. Thus the rabbit ACE-2 protein appears to be able to act as a functional receptor for the virus (despite the medium efficiency predicted by Damas et al. (2020, see above). However, as with the pig ACE2 receptor, this does not mean that the rabbit will necessarily be susceptible.
The second part of the study involved experimental inoculation of rabbits with SARS-CoV-2. Initially, three rabbits were inoculated with 10^6 tissue culture infectious doses (TCID50). No clinical signs were observed during the following 21 days. However, SARS-CoV-2 RNA was detected in the throat, nose and rectum for periods of 9 (rectum)-14 (throat) days. Infectious virus was also shed from the nose for up to 7 days. Each of the animals seroconverted against the virus (as judged by a plaque reduction neutralization test). Thus, it appears that under these conditions the rabbits did become infected, although without apparent disease.
In a second experiment, three different doses of the virus were used. Animals that received 10^5 or 10^6 TCID50 shed infectious virus from the nose for some days, however animals that received 10^4 TCID50 did not shed any detectable viral RNA.
Although no viral RNA was detected in the lungs of rabbits given the highest dose of virus, evidence for increased levels of macrophages in the lungs was obtained.
It was concluded that a minimum infectious dose of 10^5 TCID was required to obtained a productive infection in rabbits (New Zealand White). Peak virus titres in the nose of inoculated rabbits were about 10^3 TCID50/ml, thus it can be expected that transmission between rabbits will be inefficient.

Conclusions

Under experimental conditions, rabbits can become infected following inoculation of at least 10^5 TCID.
No clinical disease was observed, but some shedding of infectious virus occurs for several days and the animals seroconverted.
Transmission between rabbits (not so far tested) seems likely to be inefficient due to the low levels of virus shed and the high dose of virus required for infection.

Testing of rabbits in Denmark from a farm with SARS-CoV-2 infected mink has not shown evidence for infection either by RT-PCR or by serology.

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