Host range of SARS-CoV-2 and implications for public health

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The emergence of the current global COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is zoonotic, probably originating from bats,[1] with the intermediate species as yet unidentified despite initial pointers to pangolins. Concern is growing over possible anthroponosis of SARS-CoV-2, especially in light of its recent discovery and spread on mink farms in the Netherlands and in Spain, with the suggestion that there was transmission back to humans (ie, reverse anthroponosis). This cycle of transmission on a larger scale does not bode well for the prospect of re-emergence in humans if left unchecked, unlike severe acute respiratory syndrome coronavirus (SARS-CoV).

We evaluated evidence from widely reported real-world cases and peer-reviewed articles of experimental studies premised on infection requiring interactions between the SARS-CoV-2 spike and angiotensin-converting enzyme 2 (ACE2) receptor proteins. Six in vivo studies (all with small sample sizes) involved direct animal inoculation experiments and one was an in vitro study (appendix pp 1–2). Three additional studies presented structural models to provide the groundwork for urgent critical appraisal of possible future chains of transmission (appendix p 3).

In addition to the first reports of anthroponotic infection of cats (domestic and wild) and dogs, the experimental evidence of SARS-CoV-2 infection of animals has been shown for a variety of mammals, including monkeys, ferrets, cats, and hamsters (appendix pp 1–2).[1–6] Because the main purpose of these studies is to find suitable animal models of human disease or the identification of the intermediate hosts, they do not clearly distinguish between infection, disease, and transmission; one study reported implausibly negative results across all species, in contrast to all the other studies.[7] Conflicting experimental studies were reported for pigs, where a SARS-CoV-2 inoculation showed no infection,[4] whereas the virus was found to infect HeLa cells expressing the pig ACE2 receptor.[1] The latter study[2] is supported by all three computational model predictions of infectivity in wild boar[8] and pigs.[9,10]

Where experimental data do not exist, or where they conflict, modelling the spike–ACE2 interactions, especially at the protein–protein interface, provides further evidence for the potential of infection. The results of these computational studies suggest attention should be paid to rabbits, sheep, goats, cattle, and horses because of the implications of infection (appendix p 3). These cases are further supported by data that show spike–ACE2 receptor interactions. Another important case is the absence of experimental infection of mice (and presumably rats; appendix p 1), which is also supported by computational data (appendix p 3). Although these results were negative, additional data have shown successful infection of mice by SARS-CoV-2 and clinical manifestations of COVID-19, where a selection of experiments resulted in a SARS-CoV-2 variant, which had a single amino acid substitution in the spike protein (appendix p 3). Neither experimental nor computational studies alone will confirm that a species is unable to be infected by SARS-CoV-2. The difference between infection and clinical manifestations of disease, as well as the possibility of asymptomatic cases in animals, highlights the need for a combination of approaches, including real-word epidemiology and diagnostics, requiring the sampling of large numbers of animals to determine infection.

See Online for appendix

Once SARS-CoV-2 circulates more widely beyond humans, it will be challenging to trace natural transmission between species because the viral genome is essentially identical in humans, and existing epidemiological methods of contact tracing are equipped to identify transmission between humans to interrupt it. The aforementioned studies thus prematurely categorise the risks as low, medium, or high when based on early probability estimates of simple infection. A low probability of a high-impact outcome, such as a new reservoir species also needs to be considered. Assessing these risks includes reviewing our ability to isolate, protect, or contain animals in domestic, agricultural, and wildlife settings. Domestic species whose population numbers are sufficient to act as a reservoir include cats and dogs, which is consistent with the case reports noted earlier, and studies showing or predicting infectivity. Farmed wildlife such as mink and pigs could also become reservoir species. In addition to wild bats, rodents could potentially act as a reservoir species because they have sufficient numbers and densities for continuous transmission; this possibility is supported by a modelling study[8] that

predicted squirrels to be infected, yet other studies showed a probable low or no risk of infection for mice and rats. These considerations should lead to strategies for implementing early surveillance and precautionary mitigation measures on different species.

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix 1 – Published experimental studies listed according to type and quality of methods and species identified

Article	**Animals tested**	**Source and quality of data**	**Results**
Deng et al.[7]	This paper tested many animals including wild, companion and farm – too many to list – chicken, duck, mouse, rat and pig *etc.*	Experimental *in vivo* (direct infection) and antibody used for sole method of detection presumably missing asymptomatic cases. No metadata provided including information on the numbers of animals tested, ages *etc.*	All were negative
Kim et al.[2]	Ferrets	Experimental. *in vivo* (direct infection) and RT-PCR used for detecting CoV-2	Showed infection and transmission of virus between infected and not infected animals (transmission not requiring direct contact)
Munster et al.[6]	Macaques	Experimental *in vivo* (direct infection) and RT-PCR used for detecting CoV-2	Showed infection and possibility for transmission (no direct evidence of transmission)
Rockx et al.[3]	Macaques	Experimental *in vivo* (direct infection) and RT-PCR used for detecting CoV-2	Showed infection and possibility for transmission (no direct evidence of transmission)

Shi et al.[4]	Dogs, cats, ferrets, pigs, chickens	Experimental *in vivo* (direct infection) and RT-PCR and use of antibodies used for detecting CoV-2	Infection of cats and ferrets. Respiratory droplet transmission detected in cats. Ferrets show clinical signs of infection. Virus detected in faecal samples of some of the dogs but say they are not infectious but unclear how this was determined. CoV-2 not detected in pigs and chickens.
Sia et al.[5]	Golden hamster	Experimental *in vivo* (direct infection)	Infection of golden hamsters
Zhou et al.[1]	Horseshoe bat, civet, pig and mouse	Experimental *in vitro* – protein-protein interaction of CoV-2 spike protein and ACE2	Yes to interaction between CoV-2 spike protein-ACE2 from horseshoe bat, civet and pig No interaction with mouse ACE2

Appendix 2 – Published modelling studies listed according to type and quality of methods and species identified

Article	Animals tested	Source and quality of data	Results
Luan et al.[8]	Many animals including: apes, monkeys, cat, dog/wolf, hamster, squirrel, sheep, cows, horses, stoat, civet, wild boar, polecat, pangolin, rabbit, camel, racoon, bats, mouse, rat, platypus, racoon dog, elephant, hedgehog, meerkat, kangaroo rat, guinea pig	*in silico* modelling – based on just 5 amino acids involved in binding CoV-2 spike protein and ACE2 receptor. Unclear how cut-off was determined – see differences for horseshoe bats	Yes for possible binding apes, monkeys, cat, dog/wolf, hamster, squirrel, sheep, cattle, horses, stoat, civet, wild boar, polecat, pangolin, rabbit, camel, racoon Some bats and not others – yes to hairy-eared horseshoe bat no to greater horseshoe bat. Explanation not given. No – mouse, rat, platypus, racoon dog, elephant, hedgehog, meerkat, kangaroo rat, guinea pig
Wan et al.[9]	Ape, bat, civet, mouse, rat, pig, ferret, monkey, cat	*in silico* modelling based on 5 amino acid residues at interface between CoV-2 spike protein and ACE2 receptor	Likely interaction - ape, bat, civet, pig, ferret, monkey, cat Less likely interaction – rat, mouse
Zhai et al.[10]	Chicken, duck, guinea pig, Syrian hamster, pig, horseshoe bat, civet, mouse, dog, cat, tiger, lion, ferret, cow, sheep, camel	*In silico* modelling of receptor binding domain of spike to ACE2 protein of different animals	Detailed study of interacting residues in the interface and differences in the different animals but no predictions are made for the likelihood of infections