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COVID-19 in animals: contact with humans and potential transmissions

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Abstract. In December 2019, cases of atypical pneumonia were diagnosed in hospital patients in Wuhan, Hubei province, China. The disease was characterised by a respiratory disorder of variable severity ranging from mild upper respiratory tract illness to acute respiratory distress syndrome, severe interstitial pneumonia and death. The source of the virus is yet to be confirmed but wild animals sold at wholesale seafood and exotic animal markets of Wuhan were implicated. The virus was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease designated as Coronavirus disease-19 (COVID-19). As of the 13 January 2021, the WHO had reported 90 335 008 cases and 1 954 336 deaths in 216 countries. The isolation of related coronaviruses from bats suggests that they may be a potential host species. This paper is a review of the current literature on SARS-CoV-2 infections of animals and the animal challenge models for the *in-vivo* evaluation of vaccines and therapeutics.

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Introduction

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) originated from a reservoir host animal and transmitted to humans, possibly via an as yet unidentified intermediate host, then spread by human-to-human transmission. Bats have been suggested as the reservoir host of SARS-CoV-2[1]. Either a variant virus evolved in bats and/or the intermediate host before transmission to humans or the virus transmitted to humans as a bat or intermediate host virus and evolved in humans. The SARS-CoV-2 genome showed 88% homology with Chinese bat coronaviruses, 79% homology with SARS-CoV and 50% homology with MERS-CoV, which suggests the former[2,3]. Natural SARS-CoV-2 infections have been reported in cats, dogs, mink, tigers, and lions and experimental infections in mice, hamsters, cats, ferrets, non-human primates, and tree shrews. Animals such as poultry, bats, snakes, frogs, rabbits, marmots, and hedgehogs are sold for human consumption in the Wuhan wet markets, any of which might act as intermediate hosts. It is essential to identify any potential intermediate hosts to assist with the control of the spread of the virus and future disease outbreaks. There is an important need to develop animal challenge models that mimic the clinical and pathological presentation of human COVID-19 disease to assess vaccine efficacy and test therapeutic drugs.

Non-human primates

Many species of non-human primates have been used in studies of SARS-CoV-2 infections. In one study rhesus macaques, crab-eating macaques, but not common marmosets infected with SARS-CoV-2 showed elevated body temperatures[1,4]. Viral RNA and live virus were detected in nasal, throat and anal swabs and lesions seen in the lungs of all 3 species. The more severe lung pathology in the rhesus and crab-eating macaques was similar to human COVID-19 disease. Other studies used rhesus macaques and cynomolgus macaques to study the pathogenesis of COVID-19[5,6]. Virus replication occurred in both the upper and lower respiratory tract. Therefore, rhesus, crab-eating and cynomolgus macaques could all act as a pathogenesis model for human COVID-19 disease and could play a major role in the epidemiology of SARS-CoV-2 and possibly transmission to humans. Importantly, two studies using the rhesus macaque disease model showed that the immunity generated following primary infection protected against re-infection[7].

Bats

The horseshoe bat is the reservoir host of SARS and MERS and bats are most likely the reservoir host of SARS-CoV-2. SARS and MERS are both transmitted from bats to humans through intermediate hosts, palm civets and camels respectively, and it is likely that SARS-CoV-2 is transmitted through an as yet unidentified intermediate host[1,5,7]. No clinical signs were observed in any experimentally infected bats but virus was isolated from nasal and tracheal samples, which is characteristic of a reservoir host[5]. Antibodies and virus were detected in in-contact bats indicating bat-to-bat transmission[8]. Egyptian fruit bats are evolutionarily distinct from the putative host,

the horseshoe bat, however the data presented indicates that bats could play a role in the replication and transmission of SARS-CoV-2.

Pangolin

Recent studies found that Malayan pangolins are infected with at least two lineages of coronaviruses. Gene sequencing showed that one virus has homologies ranging from 70% in the receptor binding domain to 96% in other parts of the genome, which lead to the theory that SARS-CoV-2 resulted from recombinations between viruses infecting bats and pangolins[2]. This percentage homology is very low when compared to the 99.52% homology between SARS-CoV and the closest civet cat isolate[2]. Therefore, pangolins are considered as a potential intermediate host for SARS-CoV-2[8], but the currently available data do not rule out a non-pangolin or bat intermediate host. Further studies are required to identify the intermediate host and to confirm their role in the origin of SARS-CoV-2 in humans.

Cats

Many species of feline have been reported to be infected with SARS-CoV-2. Studies have shown that pet cats were infected from their owners and transmitted the virus to other cats by direct contact and aerosol droplets[9]. Retrospective testing of cats in Wuhan showed that 15 of 102 (14.7%) cats sampled had SARS-CoV-2-specific antibodies, suggesting that spill over from humans to cats may be frequent[5,9,10]. These findings revealed that cats are more susceptible to SARS-CoV-2 than dogs, but with mild clinical signs and some virus shedding[11,12]. Four Malayan tigers and three African lions in the Bronx Zoo showing respiratory signs tested positive, with the virus found in respiratory tract samples. The virus was probably transmitted from an asymptomatic keeper as the genome of a tiger isolate had a high homology to human strains of the time[1,7,8]. Whether cats can play a role in virus transmission to humans or other animals is not yet clear.

Mink

SARS-CoV-2 was first diagnosed on two mink farms in the Netherlands in April 2020. The animals developed respiratory and gastrointestinal signs and mortality rates of 1.2% to 2.4%, mostly in pregnant females. Workers on the farms had previously tested positive for SARS-CoV-2[13]. After the initial SARS-CoV-2 diagnosis other mink farms in The Netherlands and other countries tested positive. Comparison of the viral sequences from mink and farm employees showed that human sequences were almost identical to the mink sequences from the same farms[1,7]. These data suggest that the source of the SARS-CoV-2 was human to mink transmission, followed by evolution while circulating in the mink population before transmission back to humans. This is the first description of animal to human transmissions of SARS-CoV-2[13]. Minks are the first intensively farmed species shown to be susceptible to infection with SARS-CoV-2, suggesting a higher susceptibility of mustelids to SARS-CoV-2 and that mink may be a better experimental infection model than ferrets. SARS-CoV-2 infections of wild mustelids are of great concern as they might become permanent reservoirs of the virus in the wild.

Ferrets

Ferrets have been historically used as an animal challenge model for studying human respiratory infections such as influenza and were shown to be highly susceptible to SARS-CoV-2 infection[4]. Virus was shed in upper respiratory samples, urine and faecal samples and transmitted from infected to in-contact ferrets through direct contact or airborne transmission[1]. The ferret is considered to be the animal most similar to human infection and transmission characteristics, but has the limitations of mild clinical signs and low virus titres in infected tissues[5,14].

Other species

Several instances of SARS-CoV-2 infection of pets and farmed animals have been reported after the owners were diagnosed with COVID-19. Multiple studies have reported detection of SARS-CoV-2 in dogs but experimental infections showed that dogs have a low susceptibility to SARS-CoV-2 and do not play a significant role in the epidemiology or transmission to humans[7–9,15]. The literature on SARS-CoV-2 in pigs is contradictory, with one study reporting no evidence of infection after intranasal challenge and a second study reporting low-level responses after experimental infection[16,17]. The results suggest that pigs are poorly susceptible to SARS-CoV-2 infection and, therefore unlikely to be important in the epidemiology of SARS-CoV-2 or in transmission to humans. In a study investigating the susceptibility of various bird species, none showed any clinical signs, virus excretion or antibodies[14]. Embryonated chicken eggs inoculated by standard routes showed no evidence of virus replication, suggesting that birds are not susceptible to infection with SARS-CoV-2 and therefore unlikely to play a role in the epidemiology of SARS-CoV-2 or transmission to humans[1,18]. Various species of rodents have been experimentally infected with SARS-CoV-2. Mice showed varying results depending on the breed of mice and the virus used[4–6,19]. Several species of hamster have demonstrated clinical disease[5,7]. Other species have been implicated in the epidemiology of SARS-CoV-2, but space restrictions do not allow these to be discussed.

Conclusions

SARS-CoV-2 has been shown to bind to the angiotensin-converting enzyme 2 (ACE2) receptor on cells, and possibly other receptors[6]. The ability of the virus to cause disease in a species depends on the number of cells expressing ACE2, the homology of the animal's ACE2 with the human receptor and the presence of host cell proteases. SARS-CoV-2 has a limited host range[9]. A recent study has shown that the proportions of cells carrying both ACE2 and protease were high in bats, mink, ferrets and cats, low in pigs, very rare in dogs and absent in chickens and ducks[18]. Therefore, the SARS-CoV-2 replicates well in bats, mink, ferrets and cats, poorly in pigs and dogs and not in chickens and ducks[1,14,18]. The results of studies reported here show that several pet animal species can be infected with SARS-CoV-2; however, there is no evidence that they have a role in epidemiology of the virus. Based on this information it is recommended that basic hygiene practices be implemented by SARS-CoV-2 infected pet owners when handling their pets and all owners before and after contact. Other animal species were reported to be susceptible to SARS-CoV-2, either by natural or experimental exposure and capable of transmitting the virus to humans. Therefore, it is recommended that owners of farmed animals also implement biosecurity and biosafety measures to minimise the risk of transmission to the animals and back to humans.

Conflicts of interest

The author declares no conflict of interest.

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Biography

Paul Selleck has been at the Australian Animal Health Laboratory, now the Australian Centre for Disease Preparedness, since 1983. In this time, he was head of the Avian Disease Diagnostic Laboratory, incorporating the National, OIE and FAO Reference Laboratory for Avian Influenza and Newcastle Disease and an OIE Reference Expert for Avian Influenza and Newcastle Disease. He was also involved in the Australian equine and swine influenza outbreaks in 2007 and 2009 respectively and has worked with Hendra, Nipah and SARS at physical containment level 4. Paul now works extensively in Asia, running training courses on biosafety and biosecurity and laboratory diagnosis. He also audits laboratories and runs training courses on quality systems and ISO laboratory accreditation.