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- Review -

One-health Approach in the Post-COVID-19 Era: Focusing on Animal Infection

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To prepare for the threat of a future epidemic in the post-COVID-19 era, research based on the one-health concept (i.e., the health of humans, animals, and the environment as "one") is essential. Cross-species infections are being identified as a result of the high infection rate and viral load of SARS-CoV-2 in humans. The possibility of transmission of SARS-CoV-2 from humans to mink has been determined. In addition, the transmission of SARS-CoV-2 from humans to cats through contact has been considered possible. The data so far show that livestock and poultry are less likely to be infected with SARS-CoV-2. However, if infections are established through a new mutation, the resulting diseases are expected to have enormous ripple effects on various fields, such as human food security, the economy, and trade. In addition, there are concerns about the endemic prospect of SARS-CoV-2 and the high accessibility of companion animals. This is because the evolution of the virus likely occurs in animal hosts. Once SARS-CoV-2 is established in other species, they might serve as intermediate hosts for the re-emergence of the virus in the human population. Thus, it is necessary to ensure a rapid response to future outbreaks by accumulating research data on the animal infection of SARS-CoV-2. These data can have implications for the development of animal models for vaccines and therapeutics against SARS-CoV-2. Therefore, in this study, epidemiological reviews were analyzed, and response strategies against SARS-CoV-2 infection in animals were presented using the One-health approach.

Key words : Animal infection, cat, mink, One-health, SARS-CoV-2

Introduction

The post-COVID-19 era refers to the era that comes after overcoming COVID-19. Changes caused by COVID-19 are becoming commonplace, suggesting that such changes due to COVID-19 are important. The One-health concept means that the health of people, the environment, and animals is one [2](Fig. 1). It can be applied to the emergence and transmission of SARS-CoV-2. Continuous mutations of viruses threaten humanity. This might be because animal habitats are reduced due to indiscriminate environmental destruction. In other words, animals with viruses might frequently come into contact with humans as their habitats decrease. Therefore, COVID-19 pandemic might has been caused by reckless development and environmental destruction in the past.

Animal behaviors are affected by the environment factors. Animals affected by the environment can then affect human behaviors. That is, if something affects the health of animals (livestock), it means that it may affect the production of livestock products (food) and human diet. Therefore, if SARS-CoV-2 is established in livestock or poultry, it will exhibit ripple effects on human food security with economic and trade issues [39]. Meanwhile, familiar accessibility of companion animals also needs attention to establishment of SARS-CoV-2. Since SARS-CoV-2 expectedly become endemic, it is necessary to continuously monitor and accumulate research data on animal infection for SARS-CoV-2 to respond quickly. In addition, research on animal infection of SARS-CoV-2 is important in various ways such as the development of animal models for research of SARS-CoV-2 vaccines and therapeutics. Therefore, animal infection is an important factor for research of SARS-CoV-2 infection. Thus, the purpose of this study is to describe epidemiologic review and response

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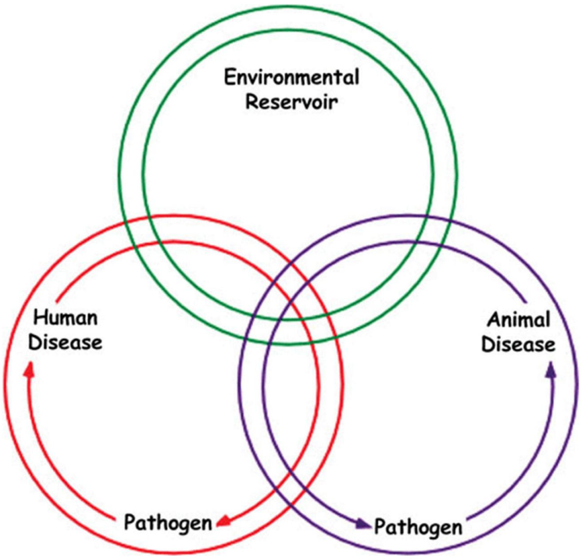

Fig. 1. The interrelationship among human disease, animal disease, and the environmental reservoir. One-health is represented by the region of overlap. doi:10.1128/microbiolspec.OH-0018-2012.f1. [2].

strategies for SARS-CoV-2 infection in animals with the One-health approach.

Cross-species infection: mechanistic review

It has been reported that SARS-CoV-2 can infect various animal species such as bats, cats, dogs, and minks, showing pantropic properties [20, 29]. In particular, its human-to-animal transmission has been identified in cats, dogs, and mink [33, 37, 48]. The evolution of viruses occurs predominantly in animal hosts with a series of genomic changes in addition to human-to-human transmission. Mutations associated with species specificity occur in the receptor-binding domain (RBD) of the spike protein, which is considerably important to do immune escape [8]. However, effects of mutations at outside of the spike protein on cross-species adaptations need further studies. The following reasons need for research on animal infection.

In the event of an animal infection, human viruses can undergo evolution that can introduce adaptive mutations. Human-to-animal infection has introduced an adaptive substitution, Y453F, resulting in the development of this variant in humans. The Y453F substitution occurred in the RBD of the spike protein. By increasing the affinity of spike protein for human ACE2, SARS-CoV-2 exhibits enhanced transmission and pathogenicity. This phenotype was found in cases of mink infection [4, 34].

Infection and transmission of SARS-CoV-2 in animals can damage human immunity and affect toxicity. It has been suggested that sequence changes, cross-species transfer, and adaptation reduce binding to monoclonal antibodies in clinical use [3, 15]. In addition, the establishment of SARS-CoV-2 in other species may provide a haven for the virus to re-emerge in the human population. Therefore, continuous research on susceptible secondary hosts is necessary.

Reported cases of SARS-CoV-2 infection in animals

Currently, SARS-CoV-2 persists through human-to-human transmission. According to genetic sequence data, the closest known relative of SARS-CoV-2 is a coronavirus that circulates in bat (*Rhinolophus*) populations [30].

Animal infection by SARS-CoV-2 has been reported in various species in several countries [29] (Table 1). The first infection of animals by transmission from humans (zoo keepers) was identified in tigers of zoos [22]. In July 2020, the transmission of SARS-CoV-2 from mink to human was ob-

Table 1. Countries report of animal type infected with SARS-CoV-2

Animal type	Infected countries*
Dog	17 countries including Argentina, Brazil, Canada, Hong Kong
Cat	21 countries including Chile, France, Russia
Tiger	6 countries, Argentina, Denmark, Indonesia, Sweden, United Kingdom, USA
Lion	8 countries including Croatia, Colombia, Singapore, USA
Puma	3 countries, Argentina, South Africa, USA
Mink (farm/wild)	12 countries including Canada, Denmark, France, Italy
Hamster	Hong Kong
Hippopotamus	Belgium
White-tailed deer	Canada, USA
Lynx	Croatia, USA
Etc. : Ferret (Slovenia), gorilla, otter, spotted hyena, coati, binturong (USA)	

* Based on animal case reports received by OMSA since March 2020 [29].

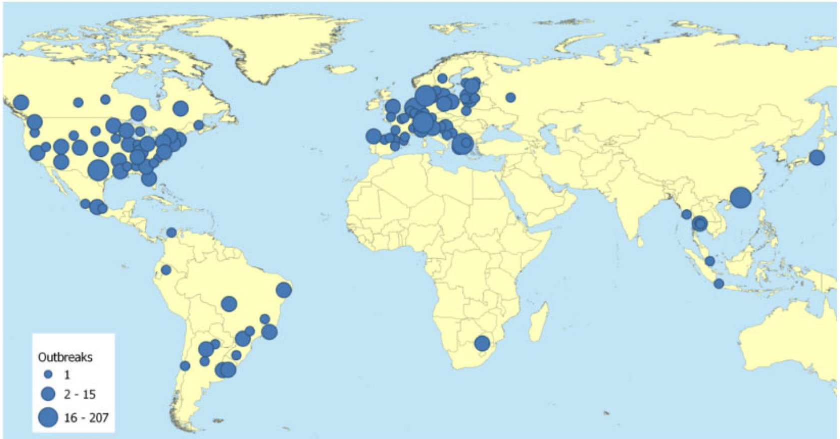

Fig. 2. The cases of animal infections with SARS-CoV-2 reported worldwide since March 2020. https://www.oie.int/es/que-ofrecemos/emergencia-y-resiliencia/covid-19/#ui-id-3. [29].

served [33, 34]. Cats and dogs, which are companion animals, sometimes can be infected through close contact with their owners [37]. Several studies have shown that pigs, mice, and poultry (chicken, duck, etc.) are not susceptible to SARS-CoV-2 infection or transmission. However, several other reports have suggested that they are sensitive [30]. Thus, further studies need to determine the potential of transmission from companion animals to humans. In addition, there have been the suggestions that animals infected with SARS-CoV-2 as food may cause transmission of the virus from animals to humans [44]. Therefore, research needs the effects of infected animal-derived foods on human infection. The World Organization for Animal Health (WOAH, founded as OIE) continuously updates cases of SARS-CoV-2 animal infection worldwide. Fig. 2 showed cases of SARS-CoV-2 animal infections reported worldwide since March 2020 [29]. There have been some cases of SARS-CoV-2 infection in cats in South Korea [14]. However, those cases were not added to OIE WOFAH data. Fig. 3 showed transmission routes of SARS-CoV-2 between human and animal species.

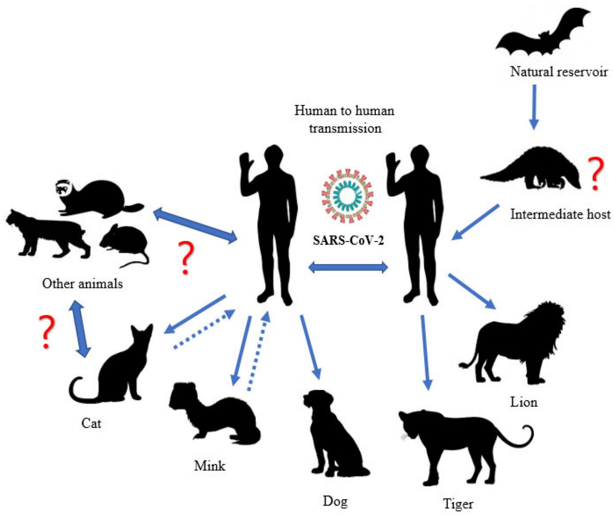

Fig. 3. Transmission routes of SARS- CoV-2 between human and animal species. SARS-CoV-2 infection in animals demonstrates reverse zoonotic transmission. Solid arrows indicate confirmed routes and dotted arrows do estimated routes. Images used in the figure were exported from Microsoft Office and Bing.

Minks

European and American minks belong to the weasel family (*Mustelidae*). They are farmed in many countries for fur. SARS-CoV-2 infection in mink was first reported in the Netherlands after separate outbreaks on two farms [33]. SARS-CoV-2 infections spread rapidly among mink housed on farms. Now SARS-CoV-2 infection in mink has been reported in 10 countries, including the United States, the Netherlands, and others [29]. Especially, with the first animal-to-human SARS-CoV-2 transmission from infected mink to farmworkers reported in the Netherlands, direct contact with mink infected with SARS-CoV-2 is considered as a risk factor for COVID-19 [34].

Indeed, SARS-CoV-2 isolated from mink and tiger showed 99.6-99.9% sequence identities with human isolates collected from around the world [41]. Following reports of human-to-mink transmission of SARS-CoV-2 have suggested that the virus has evolved due to extensive and rapid circulation between minks [34]. In addition, high diversities were identified in SARS-CoV-2 genomic sequences obtained from several mink farms. This indicates a long-term circulation of the virus among minks, which could lead to accumulation of mutations that can increase the virulence of the virus [34].

The most characteristic postmortems reported in all minks that died during SARS-CoV-2 outbreaks in the Netherlands were acute epileptic pneumonia [26]. Other consistent findings were perivascular edema, alveolar edema, and alveolar septal hyperemia. The severity of diffuse alveolar damage varied for minks from different farms. Because clinical symptoms of COVID-19 in humans and those of minks are similar, mink might be useful as an animal model to evaluate therapeutics or vaccines for COVID-19 [47].

Companion animals: Dogs and Cats

In cats and dogs, SARS-CoV-2 was detected through PCR analysis. Their clinical symptoms were generally modest and mild [32]. Dogs showed mild symptoms of SARS-CoV-2. There were reports that dogs had low susceptibility to SARS-CoV-2. At present, pets do not appear to pose a significant threat to humans for SARS-CoV-2. Therefore, always monitoring has to be conducted with potential in mind. Cats are prone to SARS-CoV-2 infection. It was shown that cats can transmit this virus to other cats [5, 12]. Cats are often asymptomatic [21, 45].

Meanwhile, in Hong Kong, nasal and oral swabs and fecal samples from clinically healthy cats were analyzed to be positive for SARS-CoV-2 by qRT-PCR [6]. In March 2020, SARS-CoV-2 RNA was detected by qRT-PCR in feces of a cat suffering from diarrhea, vomiting, and breathing difficulties in Belgium [28]. Although the cat's guardian was infected with COVID-19, genome sequences of SARS-CoV-2 present in the cat and those of the infected human did not share homogeneity. The cat showed improved symptoms 9 days after symptom onset [28]. In April 2020, a female cat of a European breed from France showed positive for SARS-CoV-2 RNA by qRT-PCR with a rectal swab. The cat exhibited clinical signs such as anorexia, vomiting, and cough at 17 days after its owner was tested positive for COVID-19 [40]. Antibodies to SARS-CoV-2 were detected in two separate serum samples. It was not surprising that cats showed clinical signs. SARS-CoV-2 can bind to the ACE2 receptor and penetrate the cell. The ACE2 receptor in cats shares high homogeneity with the human ACE2 receptor [10, 19, 51]. Experimentally infected cats could transmit SARS-CoV-2 to disease-prone cats through air particles [45]. In addition, one experimental study has shown that SARS-CoV-2 could be transmitted from virus-inoculated cats to previously uninfected cats by contacting each other. At 24 days after inoculation, all cats exhibited IgG antibody titers ranging from 5,120 to 20,480 [12]. Since cats showed no clinical signs, it suggested that cats might be quiet intermediate hosts for SARS-CoV-2 [12].

A case of SARS-CoV-2 B.1.1.7 variant of concern (VOC) strain infection in companion animals was also reported in the United States in June 2021 [13]. Two separate dogs and cats living with a COVID-19 patient in Texas, USA, were confirmed to be infected with SARS-CoV-2 B.1.1.7 (VOC). It was sampled two days after the human patient was tested positive for COVID-19. Oral, nasal, and fur swabs from both companion animals were positive for SARS-CoV-2 by qRT-PCR. Consensus whole genome sequences of dogs and cats were 100% identical, consistent with the SARS-CoV-2 B.1.1.7 (VOC). In companion animals in the United States, the first genome recovery and separation of the variant can appear as a global concern in all animals [13]. These results suggested that it is important for public health guidelines to recommend that people infected with COVID-19 should be isolated from animals and continue to apply the One-health approach to SARS-CoV-2 investigations. Concerns about future transmission of other mutations from animals to human and research on them should continue.

Research Cases of Companion Animals as Animal Models

Juvenile cats are more vulnerable to SARS-CoV-2 than under-adult cats [45]. Upon experimental infection of cats with SARS-CoV-2 virus, both male and female cats were infected with the coronavirus. Adult cats showed viral shedding for 5 days after oral and nasal infection and transmitted the infection to other cats by contact [5]. SARS-CoV-2 has been isolated from upper respiratory tract tissues such as the bronchi, nasal cavity, and esophagus [5]. Cats with SARS-CoV-2 infection were clinically asymptomatic, although RNA and antigens were detected in the airway, tissues, nasal cavity, intaglio, and rectal swabs through contact transmission [9].

Livestock species: Pigs

Studies investigating the susceptibility of livestock species to SARS-CoV-2 have reported that SARS-CoV-2 has little to no infectivity to livestock. For pigs, most available data suggest that pigs are not susceptible to SARS-CoV-2. Several experimental infections performed by study groups have indicated that pigs are not susceptible to SARS-CoV-2 infection *in vivo* [42, 45]. Clinical signs and viral replication in pigs have no clear evidence. However, there have been some conflicting reports recently. A U.S. study found no evidence of clinical signs, viral replication, or SARS-CoV-2 specific antibody responses in nine five-week-old pigs when they were infected through oral, intracranial, and tracheal pathways. However, pig cell lines including pig kidney cell lines and pig testicular (ST) cell lines were easily infected [23]. Pigs at 5-6 weeks old were divided into groups of 5 pigs, which were infected with SARS-CoV-2 using an intranasal (IN), intratracheal (IT), intramuscular (IM), or intravenous (IV) route. Forty-nine pigs in the IN group were euthanized at 1 or 2 days after infection. All other pigs were done at 2 or 22 days after infection. No secretion of RNA via the nasal or rectum was detected in pigs. Proximal bronchi from single IN-inoculated pigs were SARS-CoV-2 RNA positive after 1 day. Evidence of seroconversion to SARS-CoV-2 spike glycoprotein was found at 14 and 22 days after infection. Neutralizing antibodies were detected at 22 days after infection in pigs inoculated by the parenteral route (IM or IV). These results suggest that pigs might be a good model for SARS-CoV-2 immunogenicity studies [50]. Meanwhile, infection by another bat beta coronavirus known as swine acute diarrhea syndrome coronavirus (SADS-CoV) has been proven in pigs [53]. Therefore, it will be important for future studies to address the importance of livestock and the potential sensitivity of additional pig species to SARS-CoV-2 infections due to a huge number of pigs worldwide.

Livestock species: Poultry

Homogeneity modeling of ACE2 and its binding specificity and affinity with SARS-CoV-2 spike proteins vary in sensitivity levels in poultry. Of them, turkeys have the highest sensitivity, followed by chickens and ducks [38]. However, natural infection of SARS-CoV-2 has not yet been reported in poultry. Experimental infection tests with SARS-CoV-2 in poultry with chickens, ducks, turkeys, quails, and geese have shown that these species lack susceptibility to the virus [31, 43].

Meanwhile, at least one *in silico* study using information spectrum methodology has suggested that chicken is a potentially vulnerable animal species to SARS-CoV-2 infection [49]. Some poultry species are susceptible to infection with coronaviruses, including turkey coronavirus-infected turkey (TCoV), quail coronavirus-infected quail (QCoV), Guinea foul-coronavirus-infected guinea fowl (GfCoV), and pheasant coronavirus-infected pheasant (PhCoV) [16, 35, 36, 48]. These coronaviruses can result in intestinal disease, respiratory disease, and kidney disease. Although chickens are not known to be infected with SARS-CoV-2 via the intranasal route, it cannot be ruled out that COVID-19 could have negative economic impacts on the poultry industry [11].

Ruminants: cows, sheep, goats, etc.

Coronaviruses in ruminant animals include bovine coronavirus (BCoV), which infect cows, sheep, and goats and cause breathing difficulties [7]. So far, not much researches have been performed on ruminants. However, in a recent study using 6 cows of aged 4-5 months old intranasally inoculated with SARS-CoV-2, low levels of viral replication and antibody development were reported in 2 out of 6 animals [18]. However, to date, there are no indications that cows play any role in human epidemics. There are no reports of naturally infected cows [18]. However, it suggested that close contact between infected humans and cattle can lead to human-animal infections in cattle [18]. Reasons for their low susceptibility to infection have been reported to be low expression of ACE2 in the respiratory tract of ruminant animals [52]. Studies on the susceptibility of ruminant species such as sheep and goats to SARS-CoV-2 are needed.

Fruit bats

Studies evaluating the emergence of coronaviruses in bats have shown that some of these viruses may use several orthologues of human ACE2 for docking and entry [24, 25]. Some studies have emphasized the importance of combining genetics with existing meta-analysis data to evaluate and predict the emergence and pathogenic potential of circulating animal viruses. In other words, the importance of a platform for identifying and prioritizing pre-epidemic strains lurking in animal hosts and predicting the threat to the emergence of human populations of SARS-CoV and SARS-CoV-2 have been emphasized. This is because bats are considered natural reservoirs for many coronaviruses, including SARS-CoV and SARS-CoV-2 [1, 17]. After intranasal inoculation of fruit bats (*Rousettus aegyptiacus*) with SARS-CoV-2, infection was revealed by detecting the virus by qRT-PCR, immunohistochemistry (IHC), and *in situ* hybridization (ISH). RNA has also been identified in bronchial, lung, and lung-associated lymphoid tissues. Seven out of nine bats had seroconversion. The infection occurred in one of three animals through direct contact. There were no clinical signs, although rhinitis could be detected by immunohistochemistry (IHC) [42]. These findings suggest that although *Rousettus* bats are not the original reservoir species of SARS-CoV-2, experimental infections in these fruit bats might serve as useful models for further research such as for vaccine or antiviral testing in the host.

Discussion and recommendations

Data reported so far show that the risk of spreading

SARS-CoV-2, the virus that causes COVID-19, from companion animals (dogs and cats), poultry, pigs, and ruminants to humans appears to be low. This is a very fortunate fact. Conversely, however, it has been reported that the virus can spread from person to animal through close contact. Because COVID-19 infection is widespread in human populations around the world, care must be taken to avoid transmission of COVID-19 from humans to other companion animals. Because animal susceptibility to human transmission of SARS-CoV-2 is ambiguous, we should follow recommendations presented. Such recommendations must be followed carefully. People with suspected or confirmed COVID-19 should avoid contact with animals, including companion animals, livestock, and wild animals.

The OIE WOFAH provides the following guidelines for companion animal owners [30]:

1. People suspected or confirmed to be infected with SARS-CoV-2 should avoid close contact with companion animals. If a person has to care for companion animals, the person should practice good hygiene and wear a face mask if possible.

2. Animals raised by owners infected with SARS-CoV-2 should be kept indoors following similar isolation recommendations for humans applicable in the country or region.

3. In general, basic hygiene measures should always be implemented when handling and caring for animals, including washing hands before and after handling animals, food, and/or items.

4. As usual, companion animals should avoid interacting with other animals and humans outside their homes. One should also try to maintain social distancing while walking between dogs or cats of other outside animals or walking with people. Companion animals should not be left in contact with other dogs such as street dogs and other animals in public places. Companion animals should not be left unattended in crowded places.

A wide range of mammalian species might be susceptible to SARS-CoV-2 infection. More caution is needed with wild animals as many issues remain unknown. The OIE WOFAH has developed guidelines for people who work with wildlife in the field to minimize the risk of SARS-CoV-2 transmission [27]. People should not leave human waste or objects in forested areas where they could be ingested or touched by wildlife.

It is important to understand how different animals may be affected by SARS-CoV-2 and how they may be affected if they become infected. Extensive further studies will be needed to understand the susceptibility and epidemiology of SARS-CoV-2 through animal-to-human and human-to-animal infections. It is also important to monitor and identify animal species susceptible to SARS-CoV-2. Research is needed in the direction of predicting the possibility that the virus will mutate within an animal species and the possibility that it will increase in the future even if the current sensitivity is identified as low. Most importantly, whether infected animals can spread virus infections back to humans should be investigated since there is a great ambiguity about this. In addition, it would be good to develop an appropriate animal model through search and discovery of an intermediate host that can spread infection to humans. It is also important to continue research on vaccines and therapeutics based on the genetic mechanism of the intermediate host animal.

Therefore, monitoring of SARS-CoV-2 in animals, which should be preceded by basic research, should be done continuously in a wide range. Studies and experiments using animals as food for humans are also important in the future. Currently, research on SARS-CoV-2 related animals is limited. This is partly due to a small number of investigations and experiments, which can only be performed with a small number of animals. Thus, there is still a lot of ambiguity. Overall, we should protect animals and humans from SARS-CoV-2. To protect the entire ecosystem, an appropriate investigation is required. It is important to cooperate with each other in World Health Organization, Centers for Disease Control and Prevention, Food and Drug Administraion and OIE WOFAH. It is also important to present research plans and guidelines around the world to communicate and cooperate with each other. In the post-COVID-19 era, more research studies based on the One-health concept are needed to prepare for the upcoming threat of infectious diseases with the One-health concept in mind.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : One-health 관점에서 본 Post-COVID-19 시대의 동물 감염

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Post-COVID-19 시대에 다가올 전염병의 위협에 대비하기 위해 인간, 동물, 환경의 건강이 하나라는 One-health 개념에 기반한 연구가 필수적이다. 현재 인간의 SARS-CoV-2의 높은 감염률과 바이러스 부하로 인해 종을 뛰어넘는 감염이 확인되고 있다. 대표적으로 사람에서 밍크로의 전파 가능성이 확인되었고, 밀접 접촉 중에 사람에서 고양이로 전파가 가능할 것으로 추정되고 있다. 현재까지의 자료를 통해 가축류, 가금류에서의 감염 가능성이 낮은 것으로 보여지나 새로운 변이로 인해 감염이 확립된다면 인간의 식량 안보, 경제, 무역 등 다양한 분야에 파급 효과가 클 것으로 예측된다. 또한 SARS-CoV-2의 풍토화 전망과 반려동물로의 접근성이 높다는 점 등이 우려되는 상황이다. 바이러스의 진화는 동물 숙주에서 발생할 가능성이 높고, 다른 종에서 SARS-CoV-2가 확립되면 인간 집단에 바이러스가 다시 출현할 수 있는 중간 숙주 역할을 할 수도 있기 때문이다. SARS-CoV-2의 동물 감염에 대한 연구 데이터를 지속적으로 축적하여 빠른 대응이 필요하다고 생각된다. 또한 동물 감염에 대한 연구는 SARS-CoV-2 백신 및 치료제 연구에 사용되는 동물 모델의 개발 등을 포함한 다방면에서 중요하다. 따라서 본 연구에서는 SARS-CoV-2의 동물 감염에 대해 역학 검토 및 대응 전략을 One-health 관점에서 접근하여 분석하였다.