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SARS-CoV-2: sensitivity of animal species and public health risks

Opinion of the French National Academy of Medicine and the Veterinary
Academy of France

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In December 2019, the appearance of Covid-19 (*Coronavirus disease 2019*) in the Chinese city of Wuhan recorded a new episode in the history of crossing the species barrier. By showing a 96.2% homology with the coronavirus RaTG13 present in the horseshoe bat (*Rhinolophus affinis*), analysis of the genome of the emerging virus, SARS-CoV-2, confirmed the animal origin of this new disease.

However, while this emergence appears to have originated from a live wild and domestic animal market in Wuhan, the precise origin of the human contamination by SARS-CoV-2 is not known. During the Severe Acute Respiratory Syndrome (SARS) that appeared in 2002 in Guangdong province, also due to an emerging coronavirus (SARS-CoV-1) from a live animal market, masked palm civets (*Paguma larvata*) of wild origin were quickly incriminated as an intermediate host between bats and humans. However, in Wuhan, it was not possible to identify the intermediate host of SARS-CoV-2 since the Pangolin hypothesis (*Manis pentadactyla* and *Manis javanica*) had not been definitely demonstrated.

Although the current Covid-19 pandemic demonstrates a close adaptation of SARS-CoV-2 to the human species, host specificity is not exclusive, as many domestic and wild animal species are susceptible to the infection. After the first case of contamination of a pet dog by humans observed in Hong Kong on February 26, 2020, numerous animal infections of human origin, mostly sporadic, have been reported. Conversely, no transmission of SARS-CoV-2 to humans has so far been described from pets or domestic animals (cattle, sheep, pigs, poultry), with the exception of farmed mink. In this particular case, the contamination of 12 people from infected mink on livestock farms in Denmark was due to a mutant strain of SARS-CoV-2 which could have compromised the effectiveness of

vaccines prepared from the original virus, justifying the preventive culling in all these farms.

The target of the vaccines under development is, in whole or in part, the surface glycoprotein S (S for spicule or spike) which is involved in the binding of the virus to the host cell, membrane fusion and its entry into the cell. Binding results from the interaction between a binding site located on the S protein, the receptor binding domain (RBD), and a receptor located on the surface of the cell membrane, the angiotensin-converting enzyme 2 (ACE2). The RBD of SARS-CoV-2 would have an affinity extended to ACE2 receptors present in different pet species (dogs, cats, ferrets) or breeding species (cattle, sheep, horses). The species barrier is therefore not impermeable for both SARS-CoV-1 and SARS-CoV-2, both of zoonotic origin [1]. Its crossing by SARS-CoV-2 has been observed under natural or experimental conditions in companion animals (dogs, cats, ferrets), laboratory animals or captive or non-captive wildlife animals. In case of co-infection of pets, the possibility of recombination between canine or feline pathogenic coronaviruses and SARS-CoV-2 cannot be ruled out.

Animal infections with SARS-CoV-2

1. Pets (cats, dogs, ferrets)

1.1 *Natural contamination (dogs, cats):* under natural conditions, SARS-CoV-2 infection has been observed in animals contaminated by their owners. These were sporadic cases, either asymptomatic or revealed by minor clinical signs (respiratory difficulties with coughing, diarrhea, vomiting, etc.) which were well controlled by treatment. Since February, several countries have reported the disease: China (2 dogs and 1 cat in Hong Kong), Belgium (4 cats), United States (31 cats and 24 dogs), France (2 cats), Spain (2 cats), Germany (1 cat), Russia (1 cat), United Kingdom (1 cat), Japan (4 dogs), Chile (1 cat), CoV-2-Canada (1 dog), Brazil (1 cat), Denmark (1 dog), Italy (1 dog) [2, 3, 4].

The samples (nasopharynx, oral cavity, faeces) tested by RT-PCR were generally positive for SARS-CoV-2 demonstrating the contamination of these animals but not prejudging their infection or infectivity.

A French study conducted jointly by doctors, veterinarians and virologists showed for the first time a significant circulation of SARS-CoV-2 in a pet population (34 cats and 13 dogs) whose owners were infected with Covid-19 [5]. The survey using several serological tests (Luminex technique against three different viral proteins and seroneutralization) showed a high prevalence (21% to 53%) of specific antibodies in dogs and cats from owners infected with SARS-CoV-2, whereas only one cat was tested positive in the control group (22 dogs

and 16 cats), whose owners were free of Covid-19. These data are more demonstrative than those published so far from China, Hong Kong and Italy, but no significant differences could be found between cats and dogs. These data reopen the debate on the role of companion animals in the spread of SARS-CoV-2, particularly via contamination of household members, but virological studies are still needed to characterize the infectious process in these animals and to clarify their capacity for viral shedding.

1.2. Experimental contaminations (cat, dog, ferret): several experimental breeding trials with Covid-19 have shown that ferrets (which are also pets) and cats can be infected, much less than dogs [6, 7, 8]. These experiments have shown the possibility of recontamination by contact with control animals in cats [9] and especially in ferrets [10].

2. Domestic animals for breeding

Under experimental conditions, pigs and poultry have been shown to be resistant to inoculation with SARS-CoV-2 [7], while rabbits (which are also pets or laboratory animals) have been shown to be susceptible [11]. In Germany, the inoculation of six cattle showed very low sensitivity, with only two of them showing virus replication and seroconversion despite the presence of antibodies against bovine coronavirus (BCoV), but without transmission to the three cattle brought into contact with the inoculated animals [12].

3. Laboratory animals

Other laboratory animals that have been shown to be sensitive to SARS-CoV-2 are the golden hamster (*Mesocricetus auratus*) [13] and the rhesus macaque (*Macaca mulatta*) [14]. Furthermore, laboratory mice and rats were found to be resistant to SARS-Cov-2 [15].

4. Wildlife animals

4.1 Wildlife in zoos or in the wild: in the United States, four tigers and three lions, probably contaminated by humans in a Bronx zoo, presented discrete respiratory symptoms [16]. Since then, a tiger and a puma have also been reported infected.

Experimentally, the deer mouse (*Peromyscus maniculatus*), of the family Cricetidae, which is widespread throughout North America and is a reservoir of the Lyme disease agent has been shown to be susceptible to SARS-CoV-2 [17]. In Germany, nine bats (fruit bats or *Rousettus aegyptiacus*) were also inoculated and replicated the virus in their first respiratory tract, also contaminating one of the three bats tested by contact [7].

4.2. Wildlife farms

4.2.1. *Raccoon dogs (Nyctereutes procyonoides)*: Researchers at the Friedrich Loeffler Institute in Germany have shown that raccoon dogs (canids bred in China for their fur) are sensitive to SARS-CoV-2 (which is not surprising since they are sensitive to SARS-CoV-1) and they can infect other breeding raccoon dogs through direct contact without showing clinical signs. These animals can be considered intermediate hosts potentially involved in the spread of Covid-19 [18]. While there are no major breeding farms of raccoon dogs in Europe or China, these animals may be found in the wild after they have been released or have escaped from zoos or laboratories (where they are used, for example, in studies on rabies). Known to be the main vectors of the rabies virus in certain Eastern European forests, they are considered as pests throughout France (Order of March 24, 2014).

4.2.2. *Minks*: although sporadic or experimental contamination of certain animal species does not lead to a demonstrated risk of human contamination, the same does not apply to mink farms. In these farms, the SARS-CoV-2 viruses are not more contagious or more virulent, but they circulate rapidly in buildings and among people living in the vicinity of the farms. The rapid contamination of mink in a farm is explained by the high sensitivity of mustelids (otters, badgers, martens, sablefish, skunks, weasels, mink, ferrets) to respiratory tropism viruses. In addition, mink farming, with its high density of animals in a closed building, promotes the production of infectious aerosols and the rapid contamination of all the animals, and even of the farming staff.

SARS-CoV-2 infections in farmed mink

1. Countries other than Denmark reporting infection in mink farms:

1.1. **The Netherlands** (128 mink farms): this is the first country to report the infection of mink farms with SARS-CoV-2 (2 on April 26, 33 August 14 and 52 on September 14). Two million minks were then eliminated as the Dutch authorities wanted to bring forward the ban on mink farms before the 2024 deadline. As of September 1, the first cases of human beings contaminated with mink were reported [19]: 66 of the 97 employees of these tested farms tested positive for CoV-2-SARS, with whole genome sequencing revealing mink related variants in 47 cases [20]. These observations confirm the risk of a SARS-CoV-2 reservoir represented by infected mink farms [24]. Despite biosecurity measures, including the culling of animals, the number of infected farms continues to rise (62 on October 6, 70 on October 29) without knowing the exact origin of the infections. According to Dutch veterinary epidemiologist Francisca Velkers, "the thriller is not yet resolved".

1.2. **Spain:** on July 16, 2020, the 100,000 minks on a farm with 90% positive animals were slaughtered.

1.3. **United States:** on October 30, 2020, 11 farms in 3 states declared to have been infected from 26 July to 29 September, with several people working on these farms having tested positive for SARS-CoV-2 [20].

1.4. **Italy:** on October 27, a mink farm was declared infected (2 samples tested positive for SARS-CoV-2 in August 2020). The Italian government limited itself to monitoring clinical cases (although many infected animals may be asymptomatic). However, an emergency ban on mink farms was requested from the Prime Minister and the Minister of Health.

1.5. **Sweden:** by October 24, 2020, the first case was reported in a farm whose owner, his father and all the animals tested positive for Covid-19. On November 6, 9 other farms were declared infected but the Swedes announced that they did not intend to eliminate their 40 mink farms (i.e. 600,000 animals) at this stage, as 80% of these animals will be killed in the next few weeks for fur production, the collection of the skins being carried out with biosecurity measures.

1.6. **Greece:** on November 13, 2020, 2 farms were declared infected [21].

1.7. **France:** among the 4 mink farms still present in our country and which were placed under veterinary supervision, one located in Eure-et-Loir was declared infected on November 22, 2020. The slaughter of all the 1,000 animals still present in the farm and the disposal of the products from these animals were ordered. In the other three farms, one is free, and tests are still under way for the other two.

2. Special case of mink farms in Denmark

Denmark, the world's largest mink producer, with 1138 farms, sounded the alarm on November 4, 2020 by announcing that it was slaughtering all the mink herds in the country to stop the spread of a mutant SARS-CoV-2 in this species, this virus having crossed the species barrier by contaminating humans (12 human cases listed). The main risk linked to this mutation was to compromise the expected protection by vaccines under development. Danish scientists have indeed observed that antibodies directed against the SARS-CoV-2 virus in convalescent persons did not fully protect against this mutant virus.

2.1 ***Evolution of the viral infection in Danish mink farms:*** the first cases of contamination, presumably of human origin, were declared in June 2020 in three mink farms, which were then closed as a precautionary measure. The nationwide virus test in 10% of the mink herds, i.e. 125 farms, was negative. Surveillance is

then implemented with sampling every 3 weeks starting in week 30. A decree is issued (decree 1172 of July 17, 2020 on COVID19 in fur animals) to prevent infection of mink herds and possible transmission to humans. A fourth farm is declared infected on August 14, 6 others on September 3. The Danes decided to stop depopulating the farms. On September 18, the Danish authorities expressed concern about the risk of mink contamination to humans and announce the first biosecurity measures to reduce the spread of SARS-CoV-2 in farms. The term "risk areas", where the increase in human cases seems to be correlated with areas having a high density of mink population, is even used. Then, as in the Netherlands, while the Danes were no longer slaughtering mink from infected farms, the number of outbreaks dangerously increased (105 farms on October 19, 175 on October 29 and 205 on November 5). As of October 28, the government still had no plans to close the breeding farms. A few days later, the brutal announcement of the transmission of mutant mink viruses to humans, which could pose a risk to public health, justified the drastic decision to cull nearly 17 million minks, i.e. all those in Danish farms.

2.2 Appearance of SARS-CoV-2 variants in minks: after the slaughter of the first three infected herds, two mutations in the gene coding for the S1 (spike) protein of the SARS-CoV-2 virus, which could present a public health risk, were reported on September 4 by the Statens Serum Institut (SSI). Virological analysis (13% of the 37 967 human isolates, i.e. 5 102, have been sequenced to date) identified 214 human cases (i.e. 4.2% of the sequenced viruses) due to variant mink-related viruses, as these cases are not epidemiologically linked to a single mink farm. Two variant viruses with a modification of the gene encoding the S1 protein have been identified: the F-spike variant virus, with a Y453F mutation, corresponding to focus 1 (cluster 1) and the DFVI-spike variant virus, with a combination of 4 mutations (69-70deltaHV, 453F, 692V and 1229I) at focus 5 (cluster 5) [20, 22]. Other variant viruses isolated from foci 3 and 4 are currently being studied in detail. In contrast to the F-Spike variant, which differs little from non-mutated SARS-CoV-2, the DFVI-spike variant replicates at high infectious levels both in cell culture and in infected persons; however, among the 12 cases diagnosed in August and September, this variant did not prove to be more pathogenic than classical SARS-CoV-2. The first tests for neutralization of the DFVI-spike variant by the sera of convalescent persons showed a difference in serum antibody levels: only sera with high antibody levels had neutralizing activity. Although these are preliminary results requiring further studies, this finding, associated with the passage of this variant in humans, triggered the alert of November 4, 2020.

2.3 Public health measures adopted by the Danish government: On November 5, Denmark reinforced biosafety measures by confining the population, i.e.

280,000 inhabitants of the area of the farms affected by the variant (outbreak 5), until December 3 [23]. Health Minister Magnus Heunicke stated that half of the 783 human cases of Covid-19 in northern Denmark were mink related. Residents of the seven affected municipalities in Northern Jutland were strongly encouraged not to leave their area, to get tested and to work at home, with a ban on travel to the restriction zone, stopping of public transport (buses, trains), closure of museums, libraries, swimming pools and gymnasiums, and limitation of public gatherings to a maximum of 10 people.

Are SARS-CoV-2 mutations in animals a risk? According to the European Report on Variant Mink Viruses [20], the information available in Denmark and the Netherlands does not show an increased risk of contagiousness compared to other human viruses, although uncertainties remain, as not all cases are detected and not all viruses are sequenced. Thus, the probability of infection by mink variants is assessed as low for the general population, moderate for populations in areas with a high concentration of mink farms and very high for people exposed to mink farms.

Minor mutations are common in coronaviruses because they are RNA viruses. Since its emergence, SARS-CoV-2 has accumulated mutations compared to the first strain (Wuhan-Hu-1) sequenced in January 2020, the protein S being the most important to consider in the context of immune protection. However, they are often of no significant consequence. It is rare for a new variant to give rise to a new genetic clade that spreads globally, but adaptation to transmission in mink populations could offer a selective advantage in areas where mink farming is practiced. The Y453F mutation of the F-spike variant virus, found in both Denmark and the Netherlands, has also been detected sporadically in Russian, South African, Swiss and US sequences with no link to Denmark and the Netherlands. This could indicate that the mutation occurs in humans or that there is a sporadic undetected mink to human transmission [20]. It is also possible that mink farm workers, sometimes of foreign origin, may promote cross-border spread of these variants when they travel or return to their country of origin, as is the case with other strains of SARS-CoV-2.

The reports published so far on SARS-CoV-2 mutations do not provide precise scientific data suggesting a real risk to public health. However, while there is no evidence that these mutants pose a real danger to humans and to the efficacy of future vaccines, the precautionary principle has prevailed. While the fear generated by the emergence of a new variant that could infect humans is not new, the history of recent epidemics reminds us that this fear is sometimes unjustified. For example, the "bird flu" that appeared in 2003 did not cause a pandemic

because the A/H5N1 virus failed to adapt to the human species and to be transmitted from person to person. But the risk of genetic recombination remains much higher among influenza A viruses, due to the segmented structure of their genome, than among coronaviruses.

In this context, the European Centre for Disease Prevention and Control (ECDC) quickly published an opinion [20] recommending:

- to early detect SARS-CoV-2 infection in mink and human cases linked to mink farms, in a "one health" approach involving animal and public health authorities, in order to react quickly and put in place biosecurity measures;
- to improve an early detection of mutations in order to rapidly report any mutation of concern with the regular sharing of sequences in open databases;
- to test all suspected cases of infection in mink, farm workers or people who visited a mink farm during the incubation period and sequence SARS-CoV-2 isolates;
- to strengthen biosecurity and control measures for farm workers and persons having access to mink premises by testing them regularly by RT-PCR, to reduce the risk of transmission of a virus from humans to animals or vice versa;
- to ensure a strict surveillance of mink farms (examination of sick animals and autopsy of dead animals) and of unharmed farms;
- to carry out a systematic genotyping of all SARS-CoV-2 isolates from infected animals (cats, dogs, and especially mink) in the area of affected farms;
- to destroy mink and raw hides from infected farms;
- to ban the circulation of live mink and processed raw hides in 2020.

Despite a limited assessment of the public health risk of the mink DFVI-spike virus due to the low number of reported human cases and the scientific data available so far, **the French National Academy of Medicine and Veterinary Academy recommend:**

- to carry out additional studies to assess the risk presented by the DFVI-spike virus;

- if these studies reveal that this variant may escape to the immune response developed against CoV-2-SARS, to assess the potential implications for diagnosis, treatment and vaccine development against Covid19;

- to monitor any new SARS-CoV-2 mutation in the S protein, whether mink-bound or not, in order to be able to adapt vaccines to these mutations as has been done in veterinary medicine for avian infectious bronchitis for decades.

- not to limit surveillance to mink farms, but to extend it to other animal species (domestic or wild) to avoid the possibility of an occult animal reservoir of SARS-CoV-2;

- to strengthen the recommended biosecurity measures for animals [24], especially minks [25];

- to improve coordination between the animal health and human health (including occupational health and safety) sectors in a "one health" context to develop effective strategies to combat the Covid-19 pandemic [26].

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