Mink, SARS-CoV-2, and the human-animal interface

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24 **ABSTRACT**

25 Mink are small carnivores of the Mustelidae family. The American mink is the most common

26 and was imported to Europe, Asia, and Latin America for breeding, as its fur is very popular.

27 Denmark, the Netherlands, and China are the biggest producers of mink. Mink farms with a

28 high population density in very small areas and a low level of genetic heterogeneity are places

29 conducive to contagion. The mink's receptor for SARS-CoV-2 is very similar to that of

30 humans. Experimental models have shown the susceptibility of the ferret, cousin of the mink,

31 to become infected with SARS-CoV-2 and to transmit it to other ferrets. On April 23, 2020,

32 for the first time, an outbreak of SARS-CoV-2 in a mink farm was reported in the

33 Netherlands. Since then, COVID-19 has reached numerous mink farms in the Netherlands,

34 Denmark, United Sates, France, Greece, Italy, Spain, Sweden, Poland, Lithuania, and Canada.

35 Not only do mink become infected from each other, but they are capable of infecting humans,

36 including with virus variants that have mutated in mink. Human infection with variant mink

37 viruses with spike mutations led to the culling in Denmark of all mink in the country. Several

38 animals can be infected with SARS-CoV-2. However, anthropo-zoonotic outbreaks have only

39 been reported in mink farms. The rapid spread of SARS-CoV-2 in mink farms raises

40 questions regarding their potential role at the onset of the pandemic and the impact of mutants

41 on viral fitness, contagiousness, pathogenicity, re-infections with different mutants,

42 immunotherapy, and vaccine efficacy.

INTRODUCTION

Since the start of the pandemic, the involvement of animals has been mentioned in its occurrence. Although the possibility of other sources has been suggested, of the first 41 people hospitalized with pneumonia who received a confirmed and official diagnosis of SARS-CoV-2 infection on January 2, 2020, two-thirds were linked to the Huanan Seafood wholesale market, Wuhan, Hubei, China (Hui et al., 2020). In addition, thirty-three of 585 (5.6%) environmental samples obtained in the market, which was billed as a live animal and seafood market, indicated evidence of SARS-CoV-2 according to the Chinese Center for Disease Control and Prevention. In addition, with coronaviruses such as SARS-CoV and MERS-CoV circulating mainly among animals, a potential link between the pneumonia epidemic and the market has been suspected, as the virus may have been transmitted to humans by an animal (Liu and Saif, 2020).

Subsequently, bats and pangolins gained attention as coronaviruses closely related to SARS-CoV-2 were detected in them (Oude Munnink et al., 2021). More recently, attention has focused on mink, and more specifically farmed mink. This interest peaked when mutants of SARS-CoV-2 were transmitted from farmed mink to humans, leading to the culling of many millions of mink, in fear that the latter would transmit strains more virulent, more contagious, or resistant to vaccines in development (Larsen and Paludan, 2020; Oude Munnink et al., 2021).

Our main objective is to review the present knowledge on mink, including their ability to be infected with SARS-CoV-2, to infect humans with variants, and the impact this may have.

ECOLOGY OF MINK WORLDWIDE

The mink, a member of the family Mustelidae

The term "mink" is usually applied to at least two different animals from the family Mustelidae; the European mink (*Mustela lutreola*) and the American mink (*Neovison vison*).

The two mink, as in other mustelids, are small carnivores with characteristically elongated bodies. Mustelids contain around 60 known species, including, in addition to mink, otter, ferret, polecat, marten, ermine, badger, sable, and wolverine (Canuti et al., 2020). Several mustelids, including mink, sable, and ermine, have been hunted since prehistoric times for their fur. One of the major economic stimuli for Russian expansion into Siberia and Far East, as well as French and English expansion in North America, was the abundance of furbearers in these territories.

Some mustelids have been domesticated. The ferret (*Mustela putorius furo*) and the tayra (*Eira barbara*) are kept as pets. The ferret has been kept in Europe for a long time; the famous Leonardo da Vinci painting of the 'Lady with an Ermine' holds in her hands the albino form of domesticated ferret. As for mink, its aggressive behavior prevents their use as pets, but their fur has led to their breeding on mink farms. In recent centuries, however, fur farming, notably of American mink, has also become widespread, and provides the majority of the fur brought to market. Mink are semi-aquatic, living along waterways. They are solitary, and rather sedentary.

Feral mink

The European mink was widely distributed over most of continental Europe a century ago (Karath, 2017; Skorupski, 2020). Currently, only a few thousand (an estimated 5,000 individuals) persist in the wild in Spain, France, and the Danube delta. In Russia, sightings have become so rare that the species is considered to be on the brink of extinction (Skorupski, 2020). The European mink now occupies less than 3% of its former habitat. It is currently considered one of the most endangered mammal species in the world (Skorupski, 2020). Reintroductions of populations have been carried out in Estonia, Germany, and Spain (Karath, 2017; Skorupski, 2020). Even if the disappearing habitat and hunting may play a role in this situation, the main cause is the introduction of the invasive American mink (Karath, 2017;

Skorupski, 2020). First imported in Europe by fur farmers for their superior pelt in the 1920s, some animals escaped and thrived in the wild. Bigger, more adaptable, more aggressive, more fertile, they have simply replaced the native species (Karath, 2017).

The American mink is native to North America, where it is found throughout Canada and most of the United States, except in Arizona and the arid parts of California, Nevada, Utah, New Mexico, and western Texas. It was deliberately introduced as a fur animal in Russia and in other parts of Europe; escapees from fur farms have established populations in England, France, Germany, Iceland, Ireland, Norway, Poland, Scotland, and Sweden (Bevanger and Henriksen, 1995; Lariviere, 2021). The ability of the species to colonize new habitats is excellent, and it is estimated that all of Sweden was invaded in approximately 35 years (Gerell, 1967). *N. vison* was also brought to South America for fur farming in the 1930s, and numerous populations have been recorded in the wild since 1960-1961 (Lariviere, 2021).

Mink farms

The American mink is currently the most important species in fur-farming operations (Tomson, 1987). The main fur producing countries are Denmark, the Netherlands, Poland, and China, where the first mink farms were established in the 1950s **(Figure 1)**. China is the leading market for fur. According to the Fur Commission USA, in 2012 the United States exports of mink pelts to China reached a record high of $215.5 million (https://furcommission.com/u-s-mink-manufacturers-eye-growing-chinese-demand-for-fur/p). At the same time, China doubled its domestic mink production, contributing to a record 80 million pelts produced worldwide.

Currently, the annual production of Chinese mink is over 20 million (20.7 in 2018); the economic benefits are considered significant (Gong et al., 2020). Overall, 95% of fur farms are concentrated in the Northern provinces: Shandong (greatest concentration), Liaoning, Heilongjiang, Jilin and Henan (Gong et al., 2020). According to the European Centre for

Disease Prevention and Control, Europe has ≈ 2,750 mink farms. There are ≈ 1,200 mink

farms in Denmark (Hammer et al., 2021); ≈ 125 in the Netherlands, with an average of 5,000

female breeding animals (Oreshkova et al., 2020); ≈ 900 in Finland; and ≈ 300 in Poland,

where data must be adjusted, as numerous mink farms have been closed in the past four years.

European production was 34.7 million mink pelts in 2018. In the United States, there are ≈

245 fur farms that produced 3.1 million pelts in 2018. In Canada, 1.76 million mink pelts

were produced in 2018 on ≈ 60 farms. In Russia, according to the Russian National

Association of Fur Breeders, published in the official journal of the Russian Federal Service

for Veterinary and Phytosanitary Supervision, "Veterinaria i zhizn", 22 enterprises in 14

regions of the country are engaged in breeding mink, with a broodstock of about 300 thousand

individuals.

Female mink are bred in March and whelp in May (Tomson, 1987). The young are weaned

in July and are then placed in individual cages to prevent fighting and damage to the fur. They

have a fur molt in early fall and are killed (pelted) when their pelt is "prime"; that is, when the

pigment has migrated from skin follicles into hair shafts. The young that are desired for

breeding are held over for the next breeding season. Hundreds to thousands of cages in close

proximity are frequently housed in a small area, in a single shelter or building. Disease

problems are those caused by intensive farming practices, marginal nutrition, and poor

sanitation. Contagion is facilitated by the proximity of animals and their low genetic diversity

(reproduction using a few males selected for their fur).

MINK AND CONTAGIOUS DISEASES

Well-known contagious diseases

Several microorganisms can affect mustelids (Canuti et al., 2020). The most studied are

those commonly found in mink on fur farms. Aleutian disease, considered as the "most

serious" infectious disease affecting farmed mink, is caused by a highly contagious and

143 environmentally resistant amdoparvovirus. The disease is characterized by a chronic wasting

144 syndrome involving disruption of the immune system, with an impact on mortality and

145 reduced mink reproduction (Gong et al., 2020). Distemper is caused by a morbillivirus. It is

146 fatal to unvaccinated mink. Dogs are the common source. However, the role of wildlife

147 reservoirs, such as the fox, has been observed during a major epidemic in mink farms in

148 Denmark. Most mink farms have outer perimeter fences to exclude feral canines from their

149 mink (Trebbien et al., 2014). Mink enteritis is caused by a highly contagious virus closely

150 related to feline panleukopenia virus and canine parvovirus type 2 (Wilson et al., 2015). In

151 outbreaks, mortality is very high, reaching 75% in weaned mink. The most common bacterial

152 diseases include type C botulism and hemorrhagic pneumonia caused by specific strains of

153 *Pseudomonas aeruginosa* (Wilson et al., 2015). Mink are also often affected by coccidiosis

154 (Tomson, 1987).

155 **Emergent contagious diseases**

156 Since 2010, new epidemics have been reported in mink farms. In 2011, a new

157 orthoreovirus was reported in mink on a farm in Hebei Province, China. Almost all mink were

158 infected, with an estimated mortality of <5% (Lian et al., 2013). In 2014, an invasive outbreak

159 of swine pseudorabies occurred in mink on a farm in Shandong Province, China, with a

160 mortality rate of 87% (3,522/4,028) (Wang et al., 2018). In 2014, Newcastle disease, due to

161 avian paramyxovirus serotype-1, was described in mink on a farm in Heilongjiang province,

162 China, responsible for hemorrhagic encephalitis and pneumonia, with a death rate of 95% in

163 the 9% of affected mink (Zhao et al., 2017). In 2015, epidemics due to an H5N1 avian virus

164 were reported in 2 mink farms, 200 km apart, in northeast China. The death rates were 56%

165 (128/230) and 64% (242/376) (Jiang et al., 2017).

166 **ZOONOTIC EPIDEMIOLOGY OF SARS-CoV-2 INFECTION**

167   Early investigations showed that human SARS-CoV-2 is closely related to the

168   MN996532_raTG13 and RmYN02 coronaviruses from the Chinese horseshoe bats

169   *Rhinolophus affinis* and *Rhinolophus malayanus,* respectively (Zhou et al., 2020a; Zhou et al.,

170   2020b). Because of the lack of evidence for direct transmission of bat coronaviruses to

171   humans (Afelt et al., 2018) and the spillover theory of zoonotic emergence that postulates an

172   animal reservoir at the origin of the zoonosis (Plowright et al., 2017), many research groups

173   worldwide have attempted to identify an intermediate susceptible animal able to pass a SARS-

174   CoV-2-like virus to humans. Snakes (*Ophiophagus hannah*) were first proposed to be the

175   possible animal reservoir (Ji et al., 2020). After this hypothesis was refuted (Callaway and

176   Cyranoski, 2020), the Malayan pangolin (*Manis javanica*), was in turn designated as the

177   intermediate host (Zhang et al., 2020). However, the pangolin hypothesis was also refuted

178   (Frutos et al., 2020b; Liu et al., 2020).

179   Soon after the identification of SARS-CoV-2, it was demonstrated that the viral receptor is

180   the human angiotensin-I-converting enzyme 2 (ACE2) (Qiu et al., 2020; Yan et al., 2020;

181   Zhao et al., 2020). ACE2 is a peptidase that controls the renin-angiotensin-aldosterone system

182   regulating blood pressure, and there is a known polymorphism of ACE2 among human

183   populations and between other species (Cao et al., 2020; Devaux et al., 2020). To resolve the

184   issue of the animal reservoir, investigations redoubled in intensity, based on knowledge that

185   the ability of SARS-CoV-2 to infect an animal must depend on several factors: contact with

186   an infected host releasing infectious particles, compatibility between the spike protein of the

187   virus and the host receptor ACE2 of the target species, body temperature, the host species

188   preferences of SARS-CoV-2, and the capacity of the virus to escape the immune system and

189   restriction factors of the new host (Uzoigwe, 2020).

190   With the availability of published crystallographic analyses that determined which amino

191   acids of ACE2 are essential for the viral spike protein attachment (Lan et al., 2020; Shang et

192 al., 2020; Yan et al., 2020), one strategy for fast identification of possible SARS-CoV-2 target

193 species was performed using *in silico* screening of species ACE2 orthologs with potential

194 high affinity for the viral spike. This *in silico* approach predicted that a very large number of

195 species are possibly susceptible to SARS-CoV-2, including humans (*Homo sapiens*),

196 monkeys (*Macaca mulatta*), cats (*Felis silvestris catus*), bats (*Rhinolophus sinicus*), pangolins

197 (*Manis javanica*), turtles (*Pelodiscus sinensis*), and many others (Devaux et al., 2020; Liu et

198 al., 2020; Luan et al., 2020; Qiu et al., 2020). A recent work scored 25 amino acids considered

199 as important for interaction between the SARS-CoV-2 spike and ACE2, and suggested that

200 252 mammal and 72 bird ACE2 orthologs could serve as entry receptors for SARS-CoV-2 in

201 animal species (Damas et al., 2020). This strongly supports the hypothesis that there is not a

202 single intermediate host, but many susceptible species, that SARS-CoV-2 circulates between

203 species in the ecosystem, and when the conditions for its dissemination are met (in particular

204 a high density of susceptible hosts), an infectious contact may be sufficient to trigger an

205 outbreak in susceptible animal or human populations (Frutos et al., 2020a).

206 Gradually, *in vitro* and *in vivo* experimental infections of animals confirmed this broad

207 spectrum of targets for SARS-CoV-2. Indeed, SARS-CoV-2 can infect a wide number of wild

208 and domesticated species (Shi et al., 2020). Based on experimental models, monkeys

209 (Munster et al., 2020; Rockx et al., 2020), ferrets (Schlottau et al., 2020), cats (Halfmann et

210 al., 2020; Shi et al., 2020), as well as raccoon and dogs (Freuling et al., 2020) are among the

211 most susceptible species, while other species such as pigs are susceptible but poorly replicate

212 the virus (Schlottau et al., 2020), and other species are resistant to infection, such as the

213 mouse (Bao et al., 2020). Since then, several reports have indicated the natural infection of

214 domestic animals, cats and dogs, by their infected owner (Leroy et al., 2020). Recently, an

215 investigation of SARS-CoV-2 and anti-SARS-CoV-2 neutralizing antibodies in 919 pets from

216 northern Italy was reported, which indicated that 3.3% of dogs and 5.8% of cats had

217 measurable neutralizing antibody titers (Patterson et al., 2020). A pet ferret with digestive

218 signs and in contact with a COVID-19 person was also detected to be positive for SARS

219 CoV-2 in Slovenia

220 (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullE

221 ventReport&reportid=37289).

222   Sporadic cases of SARS-CoV-2 infections have been reported among other members of the

223 Felidae family, specifically tigers, lions, pumas (*Puma concolor*), and snow leopards

224 (*Panthera uncia*) caged in zoos (https://www.oie.int/en/). The latter were most likely infected

225 by zoo employee infected by SARS-CoV-2 (Oude Munnink et al., 2021). More recently,

226 another member of the Hominidae family, the gorilla, was also reported to be infected with

227 SARS-CoV-2 in a zoo. Besides ferrets, other members of the Mustelidae family such as the

228 American mink (*Neovison vison*), is in vivo susceptible to SARS-CoV-2 and can transmit the

229 virus both to other susceptible animals and to humans. Mink can be infected by SARS-CoV-2

230 from infected animals and humans. They can also transmit the virus to other mink and to

231 caregivers in mink farms.

232 **EVIDENCE OF SARS-CoV-2 INFECTION IN MINK**

233   **Ferret experimental model**

234   The ferret, *Mustela putorius furo*, is another member of the genus *Mustela* in the family

235 Mustelidae, and can be considered as the "cousin" of the mink. It is also the domesticated

236 form of the European polecat. Ferrets are usually considered a good animal model for viral

237 respiratory diseases (Belser et al., 2016; Hewitt et al., 2020). Based on several experimental

238 models, ferrets were shown to be highly susceptible to SARS-CoV-2 infection (Blanco-Melo

239 et al., 2020; Hewitt et al., 2020; Kim et al., 2020; Shi et al., 2020). In most models, ferrets are

240 infected with SARS-CoV-2 via the intranasal route to better mimic the natural route of

241 infection in COVID-19 patients (Blanco-Melo et al., 2020; Hewitt et al., 2020; Kim et al.,

242   2020; Shi et al., 2020). The inoculum dose varies from 5 x 10^5 to 5.5 x 10^6 plaque-forming

243   units of the virus. Various SARS-CoV-2 strains have been used, including human strains

244   (e.g., NMC-nCoV02 (Kim et al., 2020), CTan-H (Shi et al., 2020) strains, and Victoria/1/2020

245   SARS-CoV-2 (Ryan et al., 2021)) and environmental strains (e.g., the F13-E strain collected

246   from an environmental sample in the Huanan Seafood Market in Wuhan (Shi et al., 2020)).

247   Infected ferrets usually develop mild clinical symptoms, including fever 2 to 8 days post-

248   infection, reduced activity, and occasional cough (Kim et al., 2020). Clinical signs usually

249   disappear spontaneously within two weeks of infection; no fatalities have been reported (Kim

250   et al., 2020; Ryan et al., 2021). Viral RNA can be detected in nasal washes from 2 up to 20

251   days post-infection (Kim et al., 2020; Ryan et al., 2021), with the highest viral load occurring

252   at 4 days (e.g., 3.8 $\log_{10}$ RNA copies/mL (Kim et al., 2020)), but also in blood, saliva, urine,

253   and feces. Less frequently, viral RNA was detected in lungs, kidney, intestine, and fecal

254   samples between 4 and 8 days post-infection (Kim et al., 2020). In contrast, the virus was not

255   detected in the heart, liver, spleen, pancreas, and brain samples from these animals (Shi et al.,

256   2020). Two to three weeks following infection, viral RNA was no longer detectable in nasal

257   washes or any organs (Ryan et al., 2021; Shi et al., 2020).

258   Infectious viruses could be isolated in cell cultures from nasal washes, saliva, trachea, and

259   lungs collected from 2 to 4-6 days post-infection (Kim et al., 2020). Specific

260   immunohistopathological findings have also been reported and are summarized in **Table 1**

261   (Kim et al., 2020; Ryan et al., 2021; Shi et al., 2020). Antibodies against SARS-CoV-2 were

262   detected in infected ferrets by ELISA and neutralization assays at 2-3 weeks post-infection

263   (Kim et al., 2020). Serological titers ranged from 32 to 128 at that time (Kim et al., 2020).

264   Finally, infected ferrets can also transmit SARS-CoV-2 to other ferrets, with significant

265   animal-to-animal transmission through direct contact and the aerosol route **(Table 2)** (Kim et

266   al., 2020; Richard et al., 2020; Schlottau et al., 2020).

First alert in mink

As early as April 23 and 25, 2020, two closely situated (17 km apart) mink farms in the North Brabant province of the Netherlands, housing 21,000 animals, reported increased mortality in mid-April 2020 (Oreshkova et al., 2020; Oude Munnink et al., 2021). Animal necropsy enabled the detection of SARS-CoV-2 (Molenaar et al., 2020). Post-mortem findings also showed acute interstitial pneumonia in almost all mink examined (Molenaar et al., 2020). Overall, the impact of SARS-CoV-2 infection in mink ranged from asymptomatic to death, with a spectrum similar to humans (Molenaar et al., 2020). Despite strict quarantine measures, subsequent official investigations identified additional infected farms in the same region. In farms, animal-to-animal transmission was facilitated by high animal density. From June 6, mink from infected farms were culled. In early November, Dutch health authorities decided to cull all mink in the country and ban mink farming.

Epidemiology of mink SARS-CoV-2 infection

After the first Dutch cases in April, Denmark, the largest European mink pelt producer, reported mink farm infections in May 2020 in the Jutland region (Hammer et al., 2021). In mid-June the Danish government imposed the culling of infected animals in infected farms. On November 4, 2020, due to the emergence of 12 cases of human infections caused by a mink SARS-CoV-2 variant (referred to as "Cluster 5") (Larsen and Paludan, 2020), a culling of all mink was decreed. In the Netherlands and Denmark, COVID-19 cases were diagnosed among farm workers before infections in mink were detected, suggesting that the animals were infected by humans. Human and mink viral strain genome sequences, although slightly different by a few mutations, clustered together (Oude Munnink et al., 2021).

In the United States of America, the first cases of infection in farmed mink were reported in Utah on August 17, 2020, in Wisconsin and Michigan on October 8 and 9, 2020, and in Oregon on November 27, 2020, with mortality rates of mink infected by SARS-CoV-2

292 varying according to the farms **(Table 3)**. To date, in addition to the Netherlands (69 mink

293 farms), Denmark (290 mink farms), and United States (17 mink farms), SARS-CoV-2-

294 infected farms have been reported in France (1 mink farm), Greece (22), Italy (1), Spain (1),

295 Sweden (13), Poland (1), Lithuania (2), and Canada (2) (https://www.oie.int/en/). Overall,

296 cases of infections in mink farms have been reported in Europe and North America. No cases

297 of COVID-19 infection in breeding mink have been diagnosed in Russia

298 (https://www.vetandlife.ru/vizh/sobytiya/kak-v-rossii-zashchishchayut-norkovye-fermy-ot-

299 covid-19/?sphrase_id=5987). To the best of our knowledge, no cases have been reported in

300 China.

301   In Spain and Italy, infected mink farms have been suspected to have played a role in the

302 regional spread of SARS-CoV-2. At the end of June, an outbreak of COVID-19 caused by a

303 variant named 20A-EU1 began in the Aragon region of Spain and then rapidly spread to other

304 European countries because of tourist travel (Hammer et al., 2021). The region where the

305 outbreak started is known to host several mink farms where animal infections were detected.

306 In Italy the role of mink is also suspected, as the emergence of the D614G mutation occurred

307 in the Lombardy region, where Italian mink farms are located.

308   Since August 2020, Utah has been battling outbreaks of COVID-19 in mink farms

309 (https://www.kuer.org/health-science-environment/2020-12-15/novel-coronavirus-detected-

310 in-a-wild-mink-near-infected-utah-fur-farm). A state veterinarian said in November that

311 nearly 11,000 mink have died from the disease. In mid-December, a wild mink, found while

312 federal officials were surveying the area around these farms for the virus, tested positive for

313 the SARS-CoV-2. It is believed to be the first confirmed case in a free-ranging native animal.

314 A report on December 13, 2020 from the United States Department of Agriculture suggests

315 the animal acquired its infection from farmed mink. The wild animal harbored a virus that

316 appears identical to what was seen in nearby farmed mink (https://promedmail.org/promed-

317 post/?id=8015608).

MINK SARS-CoV-2 VIRUS PHYLOGENY

319   Currently, 812 mink SARS-CoV-2 genomes are available in the GISAID (Global Initiative

320 on Sharing Avian Influenza Data) database (https://www.gisaid.org/; 02/02/2021). Overall,

321 there is great genetic diversity of mink viruses. Phylogenetic reconstruction (Katoh and

322 Standley, 2013; Minh et al., 2020) based on SARS-CoV2 isolated from mink and humans has

323 revealed distinct clades (see **Figure 4**). Isolates from mink were divided into five and six

324 main groups of samples from the Netherlands and Denmark, respectively. Interestingly, we

325 observed a common node between genomes from mink, from variants 20A.EU2-Marseille-4,

326 Marseille-5, Marseille-6, and from variant 20H/501Y.V2 from England. This node pointed to

327 a common mutation in G25563U/Q57H in ORF3a of the SARS-CoV2 genome. ORF3a

328 encodes a protein with three transmembrane domains and a large cytoplasmic domain and

329 may play a structural role in the viral life cycle of SARS-CoV. Previous studies have also

330 reported that ORF3a can induce apoptosis in cells and therefore may be involved in pro-

331 apoptotic activity (Freundt et al., 2010; Law et al., 2005). Genetic diversification is linked to

332 the adaptation of the virus to a new host. Indeed, under selective pressure from the mink

333 immune system, new mutations can be fixed in the SARS-CoV-2 genome and the mink

334 SARS-CoV-2 variant virus can be introduced back into human populations.

335   About 170 mutations have been identified by whole genome sequencing of mink SARS-

336 CoV-2 samples from 40 mink farms, and mink-specific mutations of SARS-CoV-2 (including

337 a Y453F mutation in the viral spike) have been found in humans (Mallapaty, 2020). In

338 addition, 23 mutations independently appeared at least twice in SARS-CoV-2 circulating in

339 mink (https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1). The virus appears to

340 evolve at a faster rate in mink than in humans (a mutation every 2 weeks) (Oude Munnink et

al., 2021), possibly due to a phenomenon of host adaptation. Seven nonsynonymous

mutations in viral genomes from mink that independently arose at least three times are

plausible candidates for adaptation to transmission in mink. Among these, three mutations in

the receptor binding domain of the spike protein are nonsynonymous, which raises questions

about the efficacy of current vaccines in case of human infection with such strains.

HUMAN CASES

Human cases of infection from mink infected with SARS-CoV-2 that have mutated in

mink have been reported in the Netherlands and Denmark (Hammer et al., 2021; Oude

Munnink et al., 2021). In the Netherlands, 68% (66/97) of farm residents, workers, and their

contacts became infected with a mink SARS-CoV-2 variant (Oude Munnink et al., 2021). In

Denmark, sequencing of 10,386 human samples revealed SARS-CoV-2 mink-variants in 750

(7.2%) (https://www.who.int/csr/don/03-december-2020-mink-associated-sars-cov2-

denmark/en/). SARS-CoV-2 circulates rapidly in mink farms and human communities close

to farms, and 40% of human cases of COVID-19 in the North Jutland Region are with mink

variants (Larsen and Paludan, 2020). In this area, five different related clusters with several

mutations in the spike protein have been identified. In particular, one variant, "Cluster 5", has

caused alarm, as four changes in the spike protein sequence were detected (Larsen and

Paludan, 2020). Twelve human cases of infection with "Cluster 5" were identified in

September 2020 in the North Jutland area. Among them, eight had a connection to a mink

farm and four were from the local community (Larsen and Paludan, 2020).

Obviously, the risk of transmission of mink SARS-CoV-2 to humans is greatly increased

when there are large numbers of infected animals in small spaces. An infected human can

spread the mink SARS-CoV-2 variant in human populations. There is also a residual risk with

the transport of live mink (1% of the annual production, mainly breeding animals, are

transported live) which can contribute to viral spreading between farms, as well as the release

of farmed mink into the wild by animal welfare activists. Infected mink released in the wild

can infect other species, including domestic species such as cats and dogs. Fearful of seeing

SARS-CoV-2 variants selected in mink such as "Cluster 5" spread more easily among people,

and to be more deadly or to have a negative impact on the deployment of anti-COVID-19

vaccines, the Danish Government decided to cull 17 million farmed mink (Frutos and

Devaux, 2020; Koopmans, 2021). Several countries (Spain, the Netherlands, and France) have

also ordered the destruction of mink colonies infected with SARS-CoV-2.

DISCUSSION

Many species of animals can be infected with this emerging zoonosis. However, after 12

months of pandemic, among all types of farming, anthropo-zoonotic outbreaks have only been

reported in mink farms. In mink farms, contagion is facilitated by the close proximity of

animals and their low genetic diversity. They can therefore constitute a reservoir where the

virus can mutate. Infected mink can possibly be asymptomatic carriers and transmit the

SARS-CoV-2 (or new variants of this virus) to humans or animals living near farms. The

discovery of a case of COVID-19 in a wild mink in the USA raises questions about the

sustainability of a wild reservoir of SARS-CoV-2.

Currently, SARS-CoV-2 outbreaks or cases in farmed mink have been reported all over the

world, except in China and Russia. While the biggest European producers, Dutch and Danish,

have been ordered by their health authorities to kill their farmed mink and ban their breeding,

Russia has targeted the development of a vaccine for mink to prevent the spread of COVID-

19 (https://furcommission.com/). Indeed, it seems that the Federal Service for Veterinary and

Phytosanitary Supervision developed a vaccine for animals that is currently being tested

(https://www.vedomosti.ru/society/news/2020/12/11/850628-rosselhoznadzor-nazval-datu-

sozdaniya-vaktsini).

390   Overall, the rapid spread of SARS-CoV-2 in farmed mink raises many questions. First,

391   there are questions concerning a potential role in the early stages of the pandemic, especially

392   as an intermediate host. Then, there are questions concerning the rapid spread of a new virus

393   to a new host, leading to an accumulation of mutations with a potential impact on: (1) the

394   fitness of the virus; (2) its contagiousness; (3) its pathogenicity; (4) reinfections with the

395   different mutants generated; (5) effectiveness of immunotherapy; (6) and the effectiveness of

396   vaccines.

397

401   **Conflict of interest:** The authors have no conflicts of interest to declare. Funding sources

402   had no role in the design and conduct of the study

Figure Legends.

Figure 1. Distribution of the largest producers and the main mink farms worldwide.

Figure 2. Species naturally infected with SARS-CoV-2 and the origin of transmission (→).

Figure 3. Number and geographic origin of mink SARS-CoV-2 genomes available in the GISAID database (https://www.gisaid.org/; 02/02/2021). **a.** Pie chart of the number of SARS-CoV-2 genome sequences from minks per country, and proportion of the total number of SARS-CoV-2 genome sequences from minks; **b.** Temporal distribution of the number of SARS-CoV-2 genome sequences from minks per day of sample collection.

Figure 4. Mink SARS-CoV-2 virus phylogeny. A total of 744 SARS-CoV-2 were integrated in a phylogenetic analysis. All genomes were aligned by using MAFFT version 7 (Katoh and Standley, 2013). A phylogenetic tree was reconstructed by using IQ-TREE with the GTR model with ultra-fast bootstrap of 1,000 repetitions (Minh et al., 2020). Sequences of mink from the Netherlands are highlighted in yellow, those from Denmark in green. The number next to the star is the number of genomes available for each mink SARS-CoV-2 genotype.

417   **Table 1.** Histopathological abnormalities observed in an experimental ferret model.

References	Date	Main specific immunohistopathological findings
Kim et al. (Kim et al., 2020)	4 days post-infection	- Increased immune infiltration and cell debris in the alveolar wall, bronchial epithelium, and bronchial lumen, suggestive of acute bronchiolitis
	12 days post-infection	- Disappearance of pathological abnormalities
Ryan et al. (Ryan et al., 2021)	3 to 14 days post-infection	- Mild multifocal bronchopneumonia - Mild necrosis of the bronchiolar epithelial cells together with inflammatory cell infiltration of neutrophils and mononuclear cells within the bronchiolar lumina
Shi et al. (Shi et al., 2020)	13 days post-infection	- Severe lymphoplasmacytic perivasculitis and vasculitis in lungs - Increased numbers of type II pneumocytes, macrophages and neutrophils in the alveolar septa and alveolar lumen - Mild peribronchitis

418

419 **Table 2.** Evaluation of SARS-CoV-2 transmission between ferrets.

References	Infected ferrets	Transmission method	Challenged naïve ferrets
Kim et al. (Kim et al., 2020)	- All ferrets inoculated with SARS-CoV-2 developed fever at 2-8 days post-infection	**Direct contact with other infected ferrets**	- All became febrile with reduced activity 4-6 days post-contact - Most collected specimens were positive for viral RNA - Isolation of viruses from nasal washes
		Indirectly via aerosols → Different cages with a permeable partition	- None of the ferrets developed fever - Detection of viral RNA in nasal washes from only 2 of 6 ferrets with indirect contact - Positive serological titer (16) in only one
Schlottau et al. (Schlottau et al., 2020)	- Infection of 12 ferrets intranasally with 10^5 TCID$_{50}$ of viral load - None developed fever or body weight loss. - Detection of virus in nasal washes in most animals by qPCR between 2 and 8 days post-infection and culture at 2 and 4 days post-infection - All developed neutralizing antibodies	**Direct contact with other infected ferrets**	- All 3 naive ferrets acquired SARS-CoV-2 with viral RNA detection in nasal washes over 8 to 21 days post-infection - Detection of neutralizing antibodies in only one contact ferret
Richard et al. (Richard et al., 2020)	- Infection was confirmed by viral RNA shedding in nasal washes from 3 to 19 days post-infection	**Direct contact with other infected ferrets**	- Transmission to 4 of 4 naïve animals after 1-3 days. - Detection of viral RNA in newly infected ferrets up to 13-15 days post-infection
		Indirect transmission → Close but different cages	- Transmission to 3 of 4 naïve animals - Viral RNA was detected from 3-7 days post-exposure and over 13-19 days - Lower neutralizing antibody titers

420

421

422 **Table 3.** Mortality rates of mink infected by SARS-CoV-2 according to the farms in the
423 United States (US) of America.
424

Date of the outbreak	U.S. states	Number of dead mink / Number of mink in the farm	Sources
07/26/20	Utah	3,524/20,000 (16.3%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35412; https://promedmail.org/promed-post/?id=7692815
08/02/20	Utah	1,451/8,983 (16.2%)	
08/03/20	Utah	1,554/6,326 (24.6%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=35525
08/05/20	Utah	1,119/3,643 (30.7%)	
08/15/20	Utah	205/1,705 (12%)	
09/24/20	Utah	59/1,500 (3.9%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35857
09/07/20	Utah	146/600 (24.3%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35946
09/20/20	Utah	247/14,000 (1.8%)	
09/29/20	Utah	126/300 (42%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=36151
10/08/20	Utah	373/3,000 (0.1%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=36580
10/19/20	Wisconsin	2,200/22,500 (9.8%)	
10/22/20	Utah	585/13,200 (4.4%)	
10/25/20	Utah	739/38,000 (2%)	
09/27/20	Michigan	2,000/17,000 (11.8%)	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35973
09/30/20	Wisconsin	1,800/14,600 (12.3%)	
11/04/20	Wisconsin	3,400/No data available	https://promedmail.org/promed-post/?id=7923387
11/05/20	Wisconsin	2,000/No data available	
10/22/20	Oregon	No excess mortality/12,000	https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=36731

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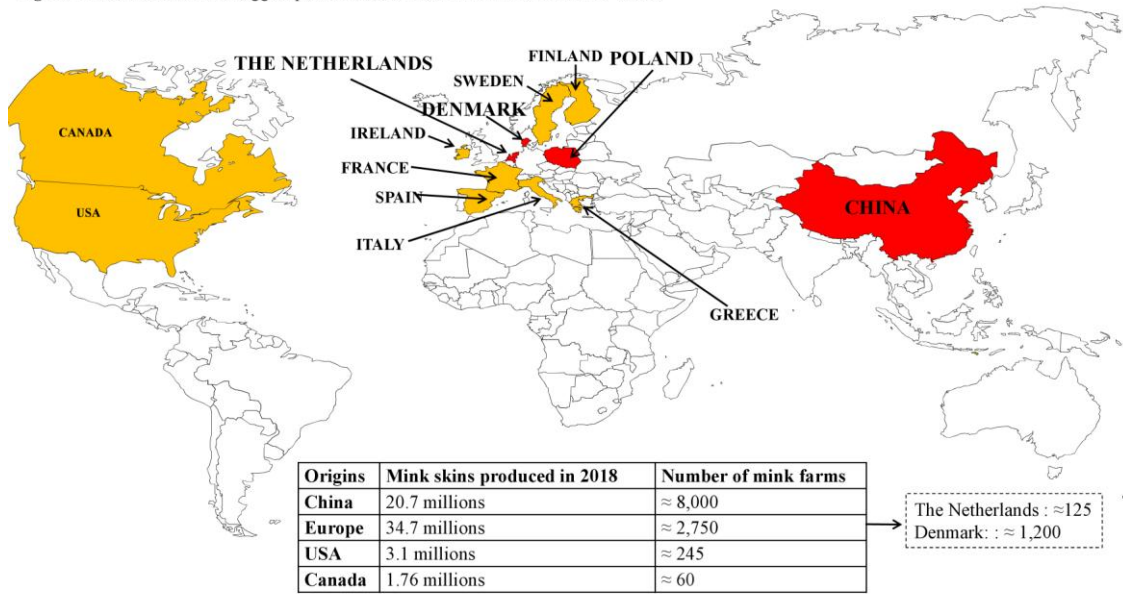596   10.1016/j.cub.2020.03.063.

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609

Figure 1. Distribution of the biggest producers and the main mink farms in the world.

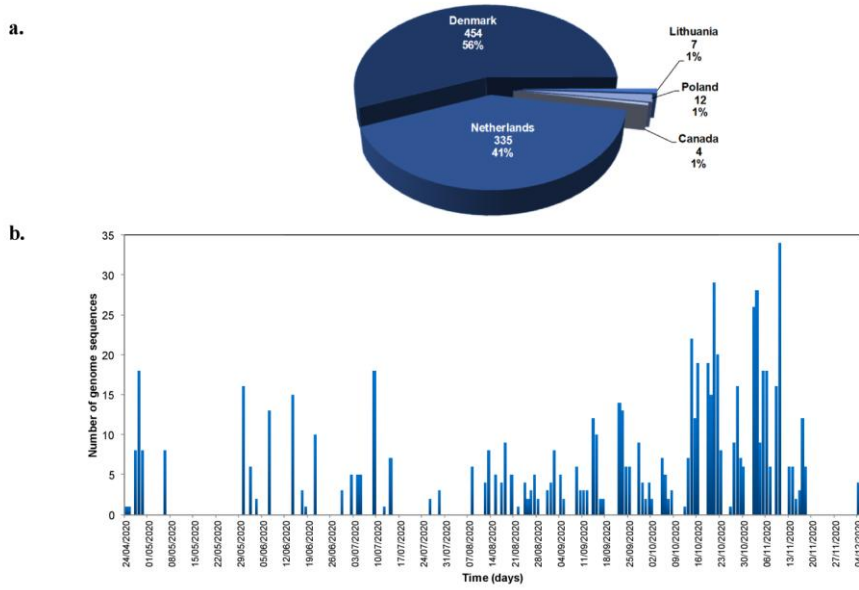| Origins	Mink skins produced in 2018	Number of mink farms
China	20.7 millions	≈ 8,000
Europe	34.7 millions	≈ 2,750
USA	3.1 millions	≈ 245
Canada	1.76 millions	≈ 60

The Netherlands : ≈125
Denmark: : ≈ 1,200

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Figure 2. Species naturally infected with SARS-CoV-2 and the origin of transmissions (→).
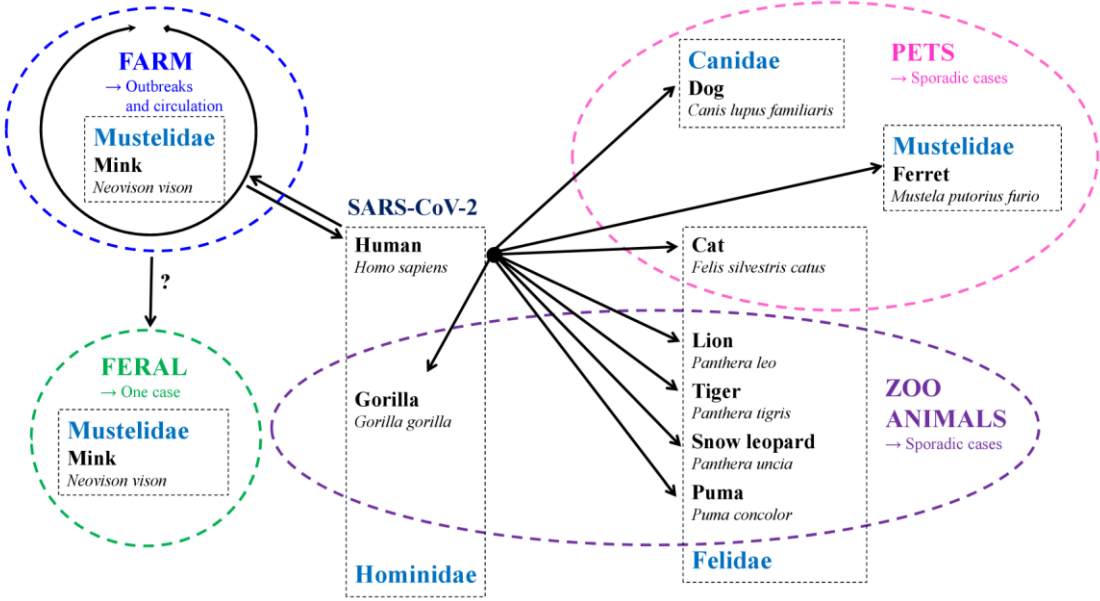
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Figure 3. Number and geographic origin of mink SARS-CoV-2 genomes available in the GISAID database (https://www.gisaid.org/; 02/02/2021).

a.

b.

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Tree scale: 0.0001

Figure 4.
Mink SARS-CoV-2 virus
phylogeny.

Wuhan/Hu-1/2019
Mink – Netherlands V1 -*35
Wuhan/WHO1/2019
Mink – Netherlands V3 -*166
Mink – Denmark V2 -*15
Mink – Netherlands V5 -*4
Marseille-6
Marseille-5
20C
20 C/501Y.V2
20A/25563T
Mink – Netherlands V2 -*62
20A/18877T
20A/26735T
Marseille-4
Marseille-2
Marseille-3
20A/15324T
Marseille-10
Mink – Netherlands V4 -*1
20A
20 A/20268G
Mink – Denmark V1 -*2
Marseille-1
Marseille-7
Marseille-8
20B
Marseille-9
Mink – Denmark V6 -*423
20I/501Y.V1 (UK)
Mink – Denmark V3 -*3
Mink – Denmark V5 -^7
Mink – Denmark V4 -*3

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