A scientific review of the role of animals farmed for fur in current and potential future pandemics of human respiratory disease
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A REPORT FOR EUROGROUP FOR ANIMALS
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EXECUTIVE SUMMARY

With more than 600 million confirmed cases since its emergence in late 2019, and more than 6.5 million deaths (and the true total may be double or even quadruple this figure), the ongoing COVID-19 pandemic has highlighted the devastating human and economic cost of emerging infectious diseases. Approximately three quarters of emerging human infectious diseases are zoonotic (originating in animals).
The major species farmed for fur are highly susceptible to SARS-CoV-2 infection

The large majority (around 90%) of fur sold globally is from farmed animals. The major species farmed for fur are American mink (Neogale vison), foxes (arctic or 'blue' foxes, Vulpes lagopus, and red or 'silver' foxes, Vulpes vulpes), and raccoon dogs (Nyctereutes procyonoides, often referred to by the fur industry as ‘Finnraccoon’ or ‘Asiatic raccoon’). Global fur production has been declining since a peak in 2014 but still involved an estimated 23 million mink, 12 million foxes and 9 million raccoon dogs in 2021. China and Europe are the largest producers of fur.

The risk of SARS-CoV-2 (the virus responsible for the COVID-19 pandemic) infection and transmission from the major species farmed for food appears to be low to negligible but the major species farmed for fur, including mink, foxes and raccoon dogs, are all highly susceptible to SARS-CoV-2 infection. Transmission to other species, including humans, has been documented in mink.

Fur-farmed species are leading candidates for an intermediate host in the emergence of the COVID-19 pandemic

The origin of the SARS-CoV-2 virus has yet to be confirmed. However, a number of authors have proposed lines of evidence implicating species farmed for fur as leading candidates for an intermediate host (linking bats and humans) in the evolution of SARS-CoV-2.

Recent studies suggest that the virus was introduced to humans in at least two separate zoonotic transmission events at the Huanan market in Wuhan around November 2019. Raccoon dogs and red foxes were observed to be present at the market during the crucial period in late 2019 and many of these animals originated from fur farms in a region with extensive cave complexes housing Rhinolophus bats, which carry SARS-related coronaviruses. Within the market, SARS-CoV-2-positive environmental samples were spatially associated with vendors selling live mammals. Given that these species are farmed in large numbers in China, are highly susceptible to SARS-CoV-2, and were being sold at the relevant time in the relevant part of the market that is implicated in the origin of the pandemic, fur-farmed species must be considered leading candidates for the zoonotic origin of the COVID-19 pandemic. Despite this, no testing and tracing of these animals has been reported.

The reclassification of fur-farmed animals as ‘special livestock’ in order to exclude them from a ban on wildlife trading in China, together with an apparent reluctance to openly investigate their possible role in the emergence of the COVID-19 pandemic, may prevent us from learning vital lessons from the current pandemic and protecting ourselves from potential future pandemics.

SARS-CoV-2 outbreaks on fur farms, emergence of new variants and transmission between mink and humans

The first recorded SARS-CoV-2 infection in mink was reported in the Netherlands in April 2020. SARS-CoV-2 has subsequently been detected in mink on hundreds of farms in Denmark, as well as on farms in Spain, USA, Italy, Sweden, Greece, France, Lithuania, Canada, Poland, and Latvia.
The transmission of SARS-CoV-2 from humans to mink, and from mink to humans, was first documented in the Netherlands and subsequently occurred many times in multiple countries. Mink-derived SARS-CoV-2 variants have been responsible for a significant proportion of human infections in some countries and regions. Mutations in the spike protein (involved in binding of the virus to host cells and the target of vaccines) in some of these variants raised concerns that mutations acquired in mink could potentially reduce the effectiveness of treatment and vaccination in humans, prompting decisions to cull millions of mink and suspend or prohibit mink farming in several countries.

Fur-farmed species could act as a reservoir of SARS-CoV-2 infection

The situation in the Netherlands and Denmark during 2020 demonstrated how SARS-CoV-2 infection could spread rapidly within and between mink farms, despite enhanced biosecurity measures and surveillance, often with unidentified modes of transmission, with repeated transmission of mink-associated variants back to humans, and was only brought under control by mass culling of all mink.

The farming of mink has continued in many other countries and new outbreaks have continued to occur, creating the possibility for farmed mink to potentially become a SARS-CoV-2 reservoir (i.e. the virus could be maintained permanently in mink farms and transmitted back to humans). There is also a risk of SARS-CoV-2 becoming established in wild/feral mink and/or other wild animals. Although COVID-19 is currently spread mostly by human-to-human transmission, the establishment of a reservoir in fur farms and/or wildlife could undermine efforts to combat the virus, by providing a source for re-emergence at any time and potentially promoting the emergence and spread of new variants.

In countries where fur farms operate, mink frequently escape into the surrounding environment. A number of SARS-CoV-2 infections have already been detected in feral American mink in the USA and Europe. The typical open-sided design of fur farms facilitates contact with wild and feral animals. If a virus reservoir is established in the wild, this poses a grave threat not only to humans but also to other wildlife species, including the critically endangered European mink (Mustela lutreola).

Fur-farmed species could act as ‘mixing vessels’ for human, avian and swine influenza viruses, promoting the emergence of new pandemic viruses

Animal species that are susceptible to co-infection with human and animal influenza A viruses can act as ‘mixing vessels’ in which novel reassortment viruses can be generated with the potential to cause pandemics.

Mink, arctic foxes and raccoon dogs possess cell receptors that make them susceptible to infection with both human and avian influenza A viruses. Influenza infections in fur-farmed species may occur with minimal or no clinical signs. Influenza in mink, foxes and raccoon dogs is not a notifiable disease and there is a lack of systematic surveillance of influenza viruses on fur farms. Reports of symptomatic influenza outbreaks on fur farms are therefore likely to represent only the tip of the iceberg. Where widescale testing of asymptomatic mink on fur farms has been carried out, farmed mink have been found to be commonly infected with multiple strains of human and avian influenza viruses. This indicates that farmed mink could be highly permissive ‘mixing vessels’ for the reassortment of circulating human and avian influenza viruses.

Potential sources of influenza infection in fur farms include raw or incompletely treated feed (especially containing poultry and/or pig meat by-products), contact with infected wild birds and/or other wildlife, and contact with infected farm workers.
Fur farms provide the ideal conditions to promote the spread of SARS-CoV-2 and influenza A viruses and the emergence of new variants

The large numbers of animals kept in crowded and chronically stressful conditions in fur farms create the perfect breeding ground for disease, including zoonotic disease. A combination of factors makes fur farms uniquely risky for public health, both within the context of the current COVID-19 pandemic, and in terms of the potential to facilitate the emergence of future pandemics. These factors include:

- **High density of animals**: typically thousands or tens of thousands per farm, housed in close confinement in adjacent cages.
- **High density of farms**: fur farms are often geographically concentrated.
- **Chronically stressful housing conditions**, potentially leading to immunosuppression.
- **Low genetic diversity** of the animals.
- **Poor biosecurity**: fur farms typically use open-sided housing, which facilitates contact with wild and feral animals, fur-farmed animals frequently escape into the surrounding environment, and fur animal feed can contain a cocktail of potentially pathogenic microorganisms.
- **Use of highly susceptible animal species**: fur-farmed species are highly susceptible to SARS-CoV-2, with the potential to form a permanent reservoir of SARS-CoV-2 infection, and are also susceptible to co-infection with a high diversity of human, avian and swine influenza A viruses, with the potential to act as ‘mixing vessels’, providing opportunities for reassortment into new viruses with pandemic potential.
- **Exposure to a high diversity of viruses**: animals on fur farms are exposed to human viruses from farm workers and to a high diversity of animal viruses through contact with wild and feral animals and the feeding of raw or inadequately treated animal products from multiple species, including poultry and pigs, in which influenza A viruses with the potential for reassortment into new viruses with pandemic potential are known to circulate.
- **Lack of systematic surveillance** of circulating influenza viruses in fur farms.

Indeed, it is hard to imagine how the fur industry could provide more ideal conditions for the emergence and spread of new viruses with pandemic potential.

Biosecurity, surveillance and vaccination programmes are not sufficient to address the public health risk from fur farms

The open-sided housing system typically used on fur farms makes it impossible to achieve a high level of biosecurity. This housing design facilitates contact with wild birds and other wild and feral animals. Even if closed housing systems were to be adopted, an exchange of pathogens with the environment can never be fully prevented.

For highly pathogenic avian influenza, domestic poultry are the main viral reservoir. Therefore, improving the biosecurity of fur farm buildings would be expected to have little impact on reducing the introduction of these viruses to fur farms when the animals are fed large quantities of raw or inadequately treated poultry by-products. Replacing raw poultry by-products in fur animal feed would likely be problematic due to negative effects on the health of the animals.

Experience to date, particularly in the Netherlands and Denmark, indicates that biosecurity measures, targeted culls and active surveillance have not been sufficient to prevent widespread SARS-CoV-2 infections on fur farms and repeated transmission of mink-associated viruses to people.

It is currently unclear to what extent vaccination of animals on fur farms might be able to reduce transmission of SARS-CoV-2 and/or influenza A viruses but vaccination comes with multiple challenges and risks and is very unlikely to be able to eliminate transmission entirely. Initial findings in relation to a SARS-CoV-2 vaccine used in mink in Finland indicate that the vaccine is unable to prevent infection.

The public health risk associated with fur farms is largely inherent in the species and the farming system used. Therefore, the farming of animals for fur poses an unacceptable public health risk that cannot be adequately mitigated. Given the non-essential nature of the product, it is hard to see how this risk can be justified.
Conclusions and recommendation

The farming of animals for fur presents an unnecessary and unacceptable risk of exacerbating the current pandemic and potentially promoting the emergence of future pandemics of human respiratory disease.

This risk to public health is largely inherent in the species and farming system used by the fur industry and cannot therefore be adequately mitigated.

The gravity of the threat, combined with the non-essential nature of the product, brings a new urgency to the need for a complete ban on the farming of animals for fur and the sale of fur products in the European Union and across the world.
INTRODUCTION

With more than 600 million confirmed cases since its emergence in late 2019, and more than 6.5 million deaths\(^1\) (and the true total may be double or even quadruple this figure\(^2\)), the ongoing COVID-19 pandemic has highlighted the devastating human and economic cost of emerging infectious diseases. Approximately three quarters of emerging human infectious diseases are zoonotic (originating in animals).\(^3\) Zoonotic viruses are the most frequently emerging human pathogen, constituting less than 15% of all known species of human pathogens, but over 65% of pathogens discovered since 1980.\(^4\) Since the second world war, agricultural expansion and intensification, including the industrialisation of animal farming, has been associated with more than 25% of all, and more than 50% of zoonotic, infectious diseases that have emerged in humans.\(^5\)

This report examines the role of animals farmed for fur in the COVID-19 pandemic and their potential role in the emergence of future pandemics of human respiratory disease.
SECTION 2:
Scale of the fur farming industry in Europe and the world

Around 90% of fur sold globally is from farming, with the remainder from trapping and hunting wild animals. American mink (*Neogale vison*) account for the largest share of global fur production, followed by foxes (arctic or ‘blue’ foxes, *Vulpes lagopus*, and red or ‘silver’ foxes, *Vulpes vulpes*) and raccoon dogs (*Nyctereutes procyonoides*, often referred to by the fur industry as ‘Finnraccoon’ or ‘Asian raccoon’). Smaller numbers of other species are also farmed for fur, including chinchilla (*Chinchilla lanigera*), sable (*Martes zibellina*), ferret (*Mustela putorius furo*) and coypu (*Myocastor coypus*). Around 650 million rabbits are reared each year worldwide, primarily for meat but some are bred for fur.

Prior to the COVID-19 pandemic, an estimated 48 million mink, 16 million foxes, and 14 million raccoon dogs were killed to supply the global fur trade in 2019. Following large-scale mink culls (see Section 5 and Table 5.1), global mink production fell sharply in 2020 to an estimated 33 million, and is expected to have fallen further in 2021 to around 23 million. Even before the pandemic, the fur industry was already in steep decline from a peak in 2014, when global annual supply reached an estimated 114 million mink, 12 million foxes, and 14 million raccoon dogs. The fall in mink production is largely responsible for the rapid decline, although annual production of foxes has also declined from a later peak of around 20 million in 2018 to around 12 million in 2021, and annual production of raccoon dogs has declined from a peak of around 16 million in 2015 to around 9 million in 2021.

China and Europe are the largest producers of fur. In 2019, Denmark was the largest producer of mink globally, before all of the estimated 15.7 million mink in the country were culled (of which around 7.4 million were used for the supply of fur and 8.3 million were destroyed). China is currently the largest producer of mink, foxes and raccoon dogs, as well as being the largest consumer of fur. There is some uncertainty regarding mink production data for China, with industry estimates of global mink production sometimes presenting lower figures for Chinese production than those reported by China. According to figures published by the China Fur Breeder’s Commission of the China Leather Industry Association, Chinese mink pelt production was 6.87 million in 2021 (down from a high of 60 million in 2014). Within Europe, annual mink production has fallen from 45 million in 2014 to an estimated 12 million in 2021 and Poland is currently the largest mink producer, following the cull in Denmark (see Table 2.1). It seems unlikely that mink production in Denmark will return to anywhere near pre-pandemic levels. Only around 1% of mink farms in Denmark (equivalent to 13 farms) have applied for compensation to enable them to keep their businesses dormant and restart operations when mink breeding is permitted to resume in Denmark, while 1,246 farms have applied for compensation to close their businesses. Other significant mink producers globally include the USA (1.4 million pelts in 2021, down from 2.7 million in 2019), Russia (1.3 million pelts in 2021), and Canada (1 million pelts in 2020).
Table 2.1.

Number of farmed mink killed for fur production in Europe at the industry's peak (2014), prior to the coronavirus pandemic (2019), and subsequently (estimated figures for 2020 and projected figures for 2021 published 27.05.21). Figures refer to mink pelt production. Totals are rounded to the nearest million. * indicates countries in which fur farming has ended or is being phased out. Source: Hansen (2021) with nationally reported figures for Denmark and Finland.  

<table>
<thead>
<tr>
<th>Country</th>
<th>2014</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>17,888,000</td>
<td>12,825,000</td>
<td>7,400,000</td>
<td>0</td>
</tr>
<tr>
<td>Poland</td>
<td>9,500,000</td>
<td>5,000,000</td>
<td>4,500,000</td>
<td>5,000,000</td>
</tr>
<tr>
<td>The Netherlands*</td>
<td>5,515,950</td>
<td>4,500,000</td>
<td>1,000,000</td>
<td>0</td>
</tr>
<tr>
<td>Finland</td>
<td>1,900,000</td>
<td>1,000,000</td>
<td>780,000</td>
<td>850,000</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1,500,000</td>
<td>1,100,000</td>
<td>1,500,000</td>
<td>1,700,000</td>
</tr>
<tr>
<td>Greece</td>
<td>1,800,000</td>
<td>1,500,000</td>
<td>1,200,000</td>
<td>1,500,000</td>
</tr>
<tr>
<td>Sweden</td>
<td>1,050,000</td>
<td>600,000</td>
<td>470,000</td>
<td>200,000</td>
</tr>
<tr>
<td>Belarus</td>
<td>900,000</td>
<td>600,000</td>
<td>750,000</td>
<td>650,000</td>
</tr>
<tr>
<td>Norway*</td>
<td>850,000</td>
<td>600,000</td>
<td>200,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Ukraine</td>
<td>750,000</td>
<td>800,000</td>
<td>1,100,000</td>
<td>1,100,000</td>
</tr>
<tr>
<td>Spain</td>
<td>700,000</td>
<td>500,000</td>
<td>450,000</td>
<td>450,000</td>
</tr>
<tr>
<td>Latvia*</td>
<td>700,000</td>
<td>500,000</td>
<td>375,000</td>
<td>360,000</td>
</tr>
<tr>
<td>Germany*</td>
<td>350,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Iceland</td>
<td>257,170</td>
<td>58,815</td>
<td>47,052</td>
<td>75,000</td>
</tr>
<tr>
<td>France*</td>
<td>200,000</td>
<td>75,000</td>
<td>32,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Italy*</td>
<td>180,000</td>
<td>120,000</td>
<td>45,000</td>
<td>0</td>
</tr>
<tr>
<td>Ireland*</td>
<td>175,000</td>
<td>90,000</td>
<td>100,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Belgium*</td>
<td>170,000</td>
<td>80,000</td>
<td>115,000</td>
<td>115,000</td>
</tr>
<tr>
<td>Estonia*</td>
<td>170,000</td>
<td>30,000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>45,000,000</strong></td>
<td><strong>30,000,000</strong></td>
<td><strong>20,000,000</strong></td>
<td><strong>12,000,000</strong></td>
</tr>
</tbody>
</table>

NB. Mink farming was suspended in Sweden in 2021, with all mink except breeding animals killed for their fur at the end of 2020 (see Table 5.1). It is unclear why a figure of 200,000 is given by Hansen for Sweden in 2021. It may be that this figure will be revised in future estimates, or it is possible this may relate to production ‘left over’ from the previous year (i.e. killed in 2020 but supplied to the market in 2021).
The large majority (around 90%) of fur sold globally is from farmed animals. The major species farmed for fur are American mink (Neogale vison), foxes (arctic or ‘blue’ foxes, Vulpes lagopus, and red or ‘silver’ foxes, Vulpes vulpes), and raccoon dogs (Nyctereutes procyonoides, often referred to by the fur industry as ‘Finnnraccoon’ or ‘Asiatic raccoon’). Global fur production has been declining since a peak in 2014 but still involved an estimated 23 million mink, 12 million foxes and 9 million raccoon dogs in 2021. China and Europe are the largest producers of fur.

China produced 11 million fox pelts and around 9 million raccoon dog pelts in 2021. Within Europe, Finland is the largest producer of foxes (mainly ‘blue’ foxes) and raccoon dogs. In 2021, Finland bred 1.18 million foxes (down from around 2 million annually prior to 2020) and 87,000 raccoon dogs (down from around 150,000 annually prior to 2020). Poland is now the second largest producer of fox pelts in Europe (30,000 pelts in 2021) following a substantial fall in production in Norway (7,000 pelts in 2021, down from 60,000 in 2020) due to the impending phase-out of the industry by 2025. Other countries where animals are farmed commercially for fur include Argentina, Cambodia, Iceland, India, Kazakhstan, Malaysia, South Africa, Thailand, Turkey, Uruguay and Vietnam.

Legislation explicitly or effectively banning fur farming of some or all species has been introduced in more than 20 countries and is currently being considered in several others.
The major species farmed for fur are highly susceptible to SARS-CoV-2 infection

The major species farmed for fur are highly susceptible to SARS-CoV-2 (the virus responsible for the COVID-19 pandemic) (see Table 3.1). There have been many outbreaks recorded on mink farms, as well as cases identified in wild/feral mink (see Section 5 and Table 5.1). Clinical signs in adult mink include laboured breathing and watery to mucoid nasal discharge, with severity ranging from barely noticeable to very severe. SARS-CoV-2 infection can induce acute severe interstitial pneumonia or diffuse alveolar damage in mink, which can cause respiratory signs and increased mortality, although infection appears to be subclinical (without observable symptoms) in some mink. Experimental infection of mink with the SARS-CoV-2 Omicron variant, which emerged in November 2021, indicates that mink are also susceptible to this variant, develop clinical signs, and are able to transmit the virus to other mink.

Experimental infection of raccoon dogs demonstrates that they are susceptible to SARS-CoV-2 infection and can transmit the virus to other raccoon dogs in neighbouring cages. Raccoon dogs showed no, or only subtle, clinical signs. Evidence was found of viral replication and tissue lesions only in the nasal conchae.

Red foxes become infected following experimental inoculation with SARS-CoV-2 and can shed virus in oral and nasal secretions. The animals exhibited mild clinical signs (lethargy/sneezing). The susceptibility of arctic foxes has not been reported but it is likely that they could also be susceptible and they have been included in trials for a COVID-19 vaccine for animals.
Ferrets are also highly susceptible to SARS-CoV-2 infection and the virus can be transmitted between ferrets through the air over more than one metre distance. Ferrets have been used as a model organism to study influenza A and SARS-CoV-1 infection due to their natural susceptibility to various human and animal respiratory pathogens and similarity to humans in lung physiology and clinical characteristics of human infectious diseases. Both mink and ferrets have been proposed as models for the study of SARS-CoV-2.

OIE guidance on working with farmed animals of species susceptible to infection with SARS-CoV-2 states: Based on current evidence, the risk of introduction of SARS-CoV-2 from people to animals is high in mustelids, including mink and ferrets, and raccoon [sic] dogs; low in rabbits; and negligible in other farmed livestock species.

### Section 3: Summary

The risk of SARS-CoV-2 infection and transmission from the major species farmed for food appears to be low to negligible but the major species farmed for fur, including mink, foxes and raccoon dogs, are all highly susceptible to SARS-CoV-2 infection. Transmission to other species, including humans, has been documented in mink.

### Table 3.1.

Susceptibility to, and transmission of, SARS-CoV-2 in the main species farmed for fur and food.

<table>
<thead>
<tr>
<th>Species</th>
<th>Type of infection recorded</th>
<th>Susceptibility to infection</th>
<th>Clinical signs</th>
<th>Transmission recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American mink</strong>&lt;br&gt;(<em>Neogale vison</em>)</td>
<td>Natural and experimental</td>
<td>Yes – high</td>
<td>Yes – in some cases</td>
<td>Yes – to other mink, to humans, and to companion animals (cats and dogs)</td>
</tr>
<tr>
<td><strong>Raccoon dogs</strong>&lt;br&gt;(<em>Nyctereutes procyonoides</em>)</td>
<td>Experimental</td>
<td>Yes – high</td>
<td>No</td>
<td>Yes – to other raccoon dogs</td>
</tr>
<tr>
<td><strong>Red fox</strong>&lt;br&gt;(<em>Vulpes vulpes</em>)</td>
<td>Experimental</td>
<td>Yes – high</td>
<td>Yes – mild</td>
<td>Not tested but experimentally infected red fox shed infectious virus for multiple days in both oral and nasal secretions, which suggests they could contribute to onward transmission of the virus</td>
</tr>
<tr>
<td><strong>Rabbits</strong>&lt;br&gt;(New Zealand White, <em>Oryctolagus cuniculus</em>)</td>
<td>Experimental</td>
<td>Yes – medium</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Pigs</strong>&lt;br&gt;(American Yorkshire crossbreed, <em>Sus scrofa</em>)</td>
<td>Experimental</td>
<td>Yes – extremely low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cattle</strong>&lt;br&gt;(<em>Bos taurus</em>)</td>
<td>Experimental</td>
<td>Yes – extremely low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Poultry</strong>&lt;br&gt;(chickens, ducks and turkeys)</td>
<td>Experimental</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Source: Adapted from OIE (2021) except red fox from Porter et al. (2022).
SECTION 4:
Fur-farmed species are leading candidates for an intermediate host in the emergence of the COVID-19 pandemic

In the past two decades, three coronaviruses with ancestral origins in bats have made the jump, with the involvement of various intermediate hosts, to cause epidemics in the human population:

- Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) emerged in 2002, possibly involving masked palm civets (*Paguma larvata*), and caused more than 8000 cases and hundreds of deaths, but was successfully contained.

- Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first identified in 2012, is thought to predominantly come from contact with dromedary camels (*Camelus dromedarius*), and continues to cause human infections, resulting in at least 2000 cases and hundreds of deaths, but infections have largely remained contained in the region around Saudi Arabia.

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which emerged in 2019, is causing an ongoing pandemic, resulting in millions of deaths and major disruption to daily life.

The origin of the SARS-CoV-2 virus has yet to be confirmed. However, recent studies implicate species farmed for fur as leading candidates for an intermediate host (linking bats and humans) in the evolution of SARS-CoV-2.

Lytras *et al.* (2021) state:

> It is currently not possible to be certain of the animal source of SARS-CoV-2, but it is notable that live animals, including civet cats, foxes, minks, and raccoon dogs, all susceptible to sarbecoviruses [a subgenus of betacoronaviruses to which SARS-CoV-2 belongs], were for sale in Wuhan markets, including the Huanan market (identified as an epicenter of the outbreak in Wuhan) throughout 2019 [...] Many of these animals are farmed for their fur at large scale and then sold to animal markets (...). Some of these farmed species (American minks, red foxes, and raccoon dogs) were sold alive for food by Wuhan animal sellers, as was trapped wildlife (including raccoon dogs and badgers), although no bat species were for sale (...). Together, this suggests a central role for SARSr-CoV–susceptible live intermediate host animals as the primary source of the SARS-CoV-2 progenitor that humans were exposed to, as was the case with the origin of SARS.
American mink, raccoon dogs and red foxes were all being sold at the Huanan Market between 2017 and 2019 and many of these animals originated from fur farms. Xiao et al. (2021) state:

While c. 30% of mammals [at the Huanan Market] were clearly wild-caught, indicated by trapping and shooting wounds, the captive breeding of other species is commonplace in China. Raccoon dog fur farming is legal in China; however, due to a drop in fur prices, raccoon dogs are now frequently sold off in live animal markets, augmented by wild-caught individuals. Similarly, all American mink (*Neovison vison*) originated from fur farms.

Analysis of the genomic diversity and epidemiology of SARS-CoV-2 early in the pandemic suggests that there were two distinct lineages (A and B) circulating in non-human mammals and introduced to humans in at least two zoonotic transmission events occurring at the Huanan market – the first, involving lineage B, estimated to have occurred in November 2019 and the second within weeks of the first.

Raccoon dogs and red foxes were observed to be present at the market during the crucial period in late 2019. Given that these species are farmed in large numbers in China (see Section 2), are highly susceptible to SARS-CoV-2 (see Section 3), and were being sold at the relevant time at a market that is implicated in the origin of the pandemic, fur-farmed species must be considered leading candidates for the zoonotic origin of the COVID-19 pandemic. Despite this, no testing and tracing of these animals has been reported. Worobey et al. (2022) state:

Although no testing of live animals for SARS-CoV-2 at the Huanan market has been reported, spatial analyses within the market show that SARS-CoV-2-positive environmental samples, including from cages, carts, and freezers, were associated with activities concentrated in the southwest corner of the market: the same section where vendors were selling live mammals, including raccoon dogs, hog badgers, and red foxes, immediately prior to the COVID-19 pandemic. Worobey et al. (2022) conclude:

...multiple plausible intermediate wildlife hosts of SARS-CoV-2 progenitor viruses, including red foxes (*Vulpes vulpes*), hog badgers (*Arctonyx albogularis*) and common raccoon dogs (*Nyctereutes procyonoides*), were sold live at the Huanan market up until at least November of 2019... No reports are known to be available for SARS-CoV-2 test results from these mammals at the Huanan market.
The preliminary report of the WHO Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) has requested further information from China regarding testing and tracing of these animals.36

According to a published survey of animals sold at the Huanan Market between 2017 and 2019, several species known to be susceptible to SARS-CoV-2 (such as raccoon dogs (Nyctereutes procyonoide), red foxes (Vulpes vulpes) and others) were present in the Huanan market (Xiao et al., 2021). However, it is noted by the SAGO that those animals were not sampled in the studies presented to the SAGO by invited Chinese scientists. The findings in Xiao et al. also correlate with a recent pre-print publication including information about animals identified at the Huanan market (Worobey et al., 2022). Further information about studies into the testing of these animals, the tracing back of these animals to source farms and serologic investigations into people who farmed and sold/traded these animals have been requested to China. Any additional findings related to these studies will be further discussed in future SAGO meetings.

In February 2020, China issued a decision banning the hunting, trading, transporting and eating the meat of wild animals in order to protect public health.37 However, commercially valuable fur-farmed species, including mink, silver foxes, arctic foxes and raccoon dogs, were subsequently reclassified as ‘special livestock’ in order to avoid the ban.38 While the ban on wildlife trading is a very welcome step in the right direction to safeguarding human health and protecting threatened species,39 the exclusion of animals farmed for fur from this ban, and apparent reluctance to openly investigate their possible role in the emergence of the COVID-19 pandemic, may prevent us from learning vital lessons from the current pandemic and protecting ourselves from potential future pandemics. Holmes et al. (2021) caution:40

Failure to comprehensively investigate the zoonotic origin through collaborative and carefully coordinated studies would leave the world vulnerable to future pandemics arising from the same human activities that have repeatedly put us on a collision course with novel viruses.

SAGO acknowledges the effort already invested in the screening of animal species with a potential to act as intermediary hosts for the virus. Even if large numbers of animals were tested in some geographical areas, the investigations in China should be better focused to include relevant mammalian target species, considering prior knowledge on disease ecology, particularly for SARS-CoV-2/SARS-CoV-like viruses. More focus is needed on studies involving carnivores in China, particularly those kept or bred in larger numbers for human exploitation, such as for food or fur production (racon [sic] dogs, civet cats, mink) in different countries and regions.
Section 4: Summary

The origin of the SARS-CoV-2 virus has yet to be confirmed. However, a number of authors have proposed lines of evidence implicating species farmed for fur as leading candidates for an intermediate host (linking bats and humans) in the evolution of SARS-CoV-2.

Recent studies suggest that the virus was introduced to humans in at least two separate zoonotic transmission events at the Huanan market in Wuhan around November 2019. Raccoon dogs and red foxes were observed to be present at the market during the crucial period in late 2019 and many of these animals originated from fur farms in a region with extensive cave complexes housing Rhinolophus bats, which carry SARS-related coronaviruses. Within the market, SARS-CoV-2-positive environmental samples were spatially associated with vendors selling live mammals. Given that these species are farmed in large numbers in China, are highly susceptible to SARS-CoV-2, and were being sold at the relevant time in the relevant part of the market that is implicated in the origin of the pandemic, fur-farmed species must be considered leading candidates for the zoonotic origin of the COVID-19 pandemic. Despite this, no testing and tracing of these animals has been reported.

The reclassification of fur-farmed animals as ‘special livestock’ in order to exclude them from a ban on wildlife trading in China, together with an apparent reluctance to openly investigate their possible role in the emergence of the COVID-19 pandemic, may prevent us from learning vital lessons from the current pandemic and protecting ourselves from potential future pandemics.
SECTION 5: SARS-CoV-2 outbreaks on fur farms, emergence of new variants and transmission between mink and humans

The first SARS-CoV-2 infection in mink was reported in the Netherlands in April 2020. SARS-CoV-2 has subsequently been detected in mink on hundreds of farms in Denmark, as well as on farms in Spain, USA, Italy, Sweden, Greece, France, Lithuania, Canada, Poland, and Latvia (See Table 5.1). No SARS-CoV-2 outbreaks have been reported on fur farms in China. However, it is not clear whether this is due to an absence of infections, a lack of appropriately targeted testing, or a lack of reporting (see Section 4).

Table 5.1. Overview of SARS-CoV-2 outbreaks in mink.

<table>
<thead>
<tr>
<th>Country (in order of first outbreak detected)</th>
<th>Overview of reported SARS-CoV-2 infections in mink (up to November 2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>Outbreaks first reported on two mink farms in April 2020. In total, 69 farms were infected. Clinical signs were reported on 29 farms. 39 outbreaks were detected by the early warning system (requirement to send in dead animals weekly). One farm was detected by serological screening. Mink were culled on 70 farms (69 infected and one with suspected infection that returned negative PCR). In December 2020, all remaining mink in the country were killed. A ban on mink farming, scheduled for 2024, was brought forward to January 2021.</td>
</tr>
<tr>
<td>Denmark</td>
<td>Outbreaks first reported on three mink farms in June 2020 and all mink on those farms were culled. Subsequently, a containment strategy was adopted with enhanced biosecurity and surveillance but no mandatory culling of infected farms. In October 2020, when 43 farms were tested positive and another 26 were under suspicion of SARS-CoV-2 infection, it was decided to cull mink on all infected farms and on farms within a 7.8km radius and surveillance was intensified. Despite these measures, new outbreaks still occurred over the next month and, by 4 November 2020, 207 farms tested positive and 23 were under suspicion. At this point, a decision was made to cull all mink in Denmark and temporarily suspend mink production. In total, 290 out of 1,140 farms were infected between June and November 2020. On one third of farms, no clinical signs were observed.</td>
</tr>
<tr>
<td>Spain</td>
<td>The first identified case in mink was in June 2020 and the infection spread to most mink on the farm by early July. Cases have been reported on 18 mink farms in total. No clinical signs were reported. Farm workers were considered likely to be the source of infection in most cases. All mink on the first three infected farms were culled. Thereafter, farms with positive cases were quarantined. Two feral American mink captured in January 2021 tested positive for SARS-CoV-2.</td>
</tr>
</tbody>
</table>

(See Table 5.1 for more details.)
<table>
<thead>
<tr>
<th>Country</th>
<th>Overview of reported SARS-CoV-2 infections in mink (up to November 2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USA</strong></td>
<td>Outbreaks reported on 18 mink farms, beginning in Utah in August 2020. High mortality of adult mink (e.g. 35-55%) reported on some farms. No mandatory culling. Free-ranging mink in the vicinity of infected farms have tested positive for SARS-CoV-2 in Utah and Oregon.</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td>First cases in mink reported on a farm in the Lombardia region in August 2020. An additional positive test was recorded from another shed on the same farm in November 2020. Surveillance of clinical symptoms combined with PCR testing on this farm proved inadequate to identify infection in most asymptomatic animals. Serological testing revealed that 100% of sera were positive for antibodies to the SARS-CoV-2 spike protein, despite only a few animals testing positive by PCR. Mink farming was suspended in November 2020 but breeding animals were permitted to remain on farms. There were further positive cases on another mink farm in March 2021. No clinical signs or increased mortality observed. A ban on fur farming was made permanent from January 2022.</td>
</tr>
<tr>
<td><strong>Sweden</strong></td>
<td>First outbreak reported on a mink farm in October 2020. Slight increase in mortality but no other clinical signs. The farm owner and his father tested positive. Movement restrictions and biosecurity measures were imposed but no mandatory culling. Infections were reported on a further nine farms in the same area in November. Infections were identified through surveillance (testing of dead mink). Movement restrictions and biosecurity measures were applied to all mink farms but no mandatory culling. Infections on a further three farms in the same area were reported in December. Mink were killed for commercial pelting during November and December 2020, leaving around 100,000 breeding mink on farms. Ongoing serological and virological sampling of remaining mink and surveillance scheme targeting humans in contact with mink. Serological screening on 26 farms in December 2020 found antibodies on 23 farms. Active surveillance programme targeting mink farm workers demonstrated a clear association between presence of SARS-CoV-2 among the mink and COVID-19 in people associated with mink, supported by the results of the whole genome sequencing. Mink breeding was temporarily suspended but breeding animals remained on farms and another farm tested positive in August 2021. The temporary ban was lifted at the end of 2021 but some restrictions remained, including that no live mink could be moved between farms in 2022.</td>
</tr>
<tr>
<td><strong>Greece</strong></td>
<td>In total, 25 out of 91 mink farms have tested positive for SARS-CoV-2 since the first outbreak was confirmed in November 2020. Epidemiological data and comparative analysis among human and mink isolated SARS-CoV-2 genomes indicate that minks were infected, in most cases, by humans. Culling of mink was only applied to the first confirmed farm. Movement restrictions and biosecurity measures have been imposed on all mink farms, plus obligatory reporting of increased mink morbidity and mortality to national veterinary authorities for investigation, and vaccination and weekly testing of mink farm owners/workers.</td>
</tr>
<tr>
<td><strong>France</strong></td>
<td>Outbreak reported on one farm in November 2020. All 4,100 mink were culled. Surveillance was implemented on the other three mink farms in the country. The farming of mink and other non-domesticated animals for fur was banned in November 2021.</td>
</tr>
<tr>
<td><strong>Lithuania</strong></td>
<td>Outbreaks reported on 17 mink farms since the first outbreak was detected in November 2020. Outbreaks were mostly identified via surveillance, sometimes without clinical signs. Infections in farm workers were detected in some cases. No mandatory culling of all mink on infected farms.</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>Outbreaks reported on three farms, beginning in November 2020. Most of the remaining mink on the farms were killed (for commercial use).</td>
</tr>
<tr>
<td><strong>Poland</strong></td>
<td>Outbreaks detected on 15 farms, beginning in January 2021. No clinical signs. The samples were collected as a part of active monitoring. Mink were culled on the first farm but not during subsequent outbreaks.</td>
</tr>
<tr>
<td><strong>Latvia</strong></td>
<td>Outbreak detected on one farm in April 2021 via monitoring programme (weekly sample of dead mink showed positive result). For confirmation, 10 additional samples (dead mink) were taken and the presence of SARS-CoV-2 virus was confirmed in nine animals. The farm housed 64,000 breeding females. No clinical signs. No mandatory culling of mink on the infected farm. A ban on fur farming was agreed in September 2022 and will come into force in 2028.</td>
</tr>
</tbody>
</table>
The transmission of SARS-CoV-2 from humans to mink, and from mink to humans, was first documented in the Netherlands and subsequently occurred many times in multiple countries. Diaz et al. (2021) state:

Reverse zoonotic transmission events (from humans to mink) have introduced the virus to farms with subsequent extensive mink-to-mink transmission as well as further zoonotic (mink-to-human) transmission events generating cases among both farm workers and the broader community.

Sustained infection and transmission of SARS-CoV-2 in mink provides an opportunity for evolutionary changes in the virus that can result in variants with potential consequences for transmissibility, pathogenicity and immune evasion in humans. Whole-genome sequencing of the virus isolated from mink on farms in the Netherlands provided evidence of both human-to-mink and mink-to-human transmission of the virus. The virus was initially introduced to mink farms by humans and subsequently evolved during widespread circulation in mink. Testing (on 16 farms) of mink farm residents, employees, and individuals with whom they had been in contact, found that 68% had evidence of SARS-CoV-2 infection, and individuals for which whole genomes were available were shown to be infected with strains with an animal sequence signature. Infected mink farms were found to be highly contaminated with SARS-CoV-2 RNA in airborne dust, especially inhalable dust, and on surfaces including mink cages, bedding material, and faecal material. Despite enhanced biosecurity, early warning surveillance, and immediate culling of animals in affected farms, transmission occurred between mink farms in multiple large transmission clusters with uncertain modes of transmission. Movement of people and distance between farms were statistically significant predictors of viral dispersal between farms. Viruses belonging to the largest cluster acquired an amino acid substitution in the receptor binding domain of the spike protein, evolved faster and spread longer and more widely. Mutations in the spike protein are of particular concern because it is involved in binding of the virus to host cells and is the target of vaccines.

At its peak, a mink-derived variant was responsible for approximately 40% of the total human cases in the Netherlands. Evidence of SARS-CoV-2 infection was found in seven of 24 stray cats tested in the vicinity of two mink farms. The sampled cats inhabited the surroundings of the farms but did not come into human dwellings. Further testing of more than 100 feral and domestic cats and 13 dogs around 10 infected mink farms showed evidence of SARS-CoV-2 infection in 12 feral cats and two dogs. A sequence generated from a cat throat swab clustered with mink sequences from the same farm. As only feral cats were infected, it is most likely that infections in cats were initiated by mink rather than humans. Sequencing of samples from humans infected with mink-related SARS-CoV-2 in Denmark revealed that the virus had accumulated mutations with potentially adverse consequences for human health. Further investigation confirmed that mutations in the mink-related ‘Cluster 5’ SARS-CoV-2 variant in Denmark did affect its susceptibility to antibodies in recovered COVID patients and vaccinated individuals. SARS-CoV-2 infections in farmed mink in Denmark and local human infection trends were significantly linked. Human incidence rates were up to 75% higher in Danish municipalities with SARS-CoV-2 outbreaks on mink farms compared to municipalities with no outbreaks of SARS-CoV-2 on mink farms. Human disease effects arrived one to three weeks after the occurrence of the first disease outbreak on a mink farm in a municipality/neighbouring municipalities. An estimated 4000 individuals were infected with mink-associated SARS-CoV-2 variants in Denmark. In the North Denmark Region, between June and November 2020, 27% of SARS-CoV-2-strains from humans in the community were mink-associated. In mink farms, SARS-CoV-2 was detected in air samples close to the mink, on mink fur, on flies, on the foot of a seagull, and in gutter water. Some dogs and cats from infected farms tested positive for the virus.

In France, the ‘Marseille-4’ variant was identified in human samples in Marseille at the end of July 2020. This mink-associated variant had 13 hallmark mutations including a substitution in the receptor binding domain of the spike protein targeted by vaccines. Marseille-4 rapidly became the predominant strain, reaching 100% of identified viral strains in the area by early November 2020, and was more frequently associated with hypoxaemia than previous strains. SARS-CoV-2 isolates from mink in Poland were also found to contain sporadic mutations throughout the full genome sequence, including in the spike protein. Mink to human transmission of a mink-associated variant, which had undergone adaptation in mink lasting at least three months, was detected in a worker employed at one of the infected farms in Poland.
The ‘Y453F’ mutation in the receptor binding domain (RBD) of the spike protein appeared independently in SARS-CoV-2 infected mink in several countries, including the Netherlands, Denmark, Sweden, Greece, Poland, and Lithuania. While Y453F is potentially an adaptation to the mink ACE2 receptor (angiotensin-converting enzyme 2 – the cell receptor where SARS-CoV-2 enters host cells), it also increases affinity for human ACE2. Hoffman et al. (2021) report that mutations frequently found in the receptor binding domain (RBD) of the spike protein of SARS-CoV-2 from mink are mostly compatible with efficient entry into human cells and that mutation Y453F reduces neutralisation by an antibody used for COVID-19 therapy and sera/plasma from COVID-19 patients compared with the original ‘wild type’ (WT) virus (see Figure 5.1). They conclude:

These results suggest that antibody responses induced upon infection or certain antibodies used for treatment might offer insufficient protection against SARS-CoV-2 variants from mink.

Section 5: Summary

The first recorded SARS-CoV-2 infection in mink was reported in the Netherlands in April 2020. SARS-CoV-2 has subsequently been detected in mink on hundreds of farms in Denmark, as well as on farms in Spain, USA, Italy, Sweden, Greece, France, Lithuania, Canada, Poland, and Latvia.

The transmission of SARS-CoV-2 from humans to mink, and from mink to humans, was first documented in the Netherlands and subsequently occurred many times in multiple countries. Mink-derived SARS-CoV-2 variants have been responsible for a significant proportion of human infections in some countries and regions. Mutations in the spike protein (involved in binding of the virus to host cells and the target of vaccines) in some of these variants raised concerns that mutations acquired in mink could potentially reduce the effectiveness of treatment and vaccination in humans, prompting decisions to cull millions of mink and suspend or prohibit mink farming in several countries.
SECTION 6: Fur-farmed species could act as a reservoir of SARS-CoV-2 infection

Haydon et al. (2002) define a reservoir as:

One or more epidemiologically connected populations or environments in which the pathogen can be permanently maintained and from which infection is transmitted to the defined target population.

The situation in the Netherlands and Denmark during 2020 (see Section 5) demonstrated how SARS-CoV-2 infection could spread rapidly within and between mink farms, despite enhanced biosecurity measures and surveillance, often with unidentified modes of transmission, with repeated transmission of mink-associated variants back to humans, and was only brought under control by mass culling of all mink. Large numbers of kits, naïve to infection, are born on fur farms every year, and there is evidence that mink can sometimes be re-infected with SARS-CoV-2 following recovery from an initial infection (see Section 9). These factors suggest that there would be a ready supply of new hosts to potentially allow continued circulation of the virus in fur farms indefinitely. Shuai et al. (2021) state:

If infection by SARS-CoV-2 spills into wild mustelids, these have the potential to become a permanent reservoir of infection for other animal species. Such a scenario has been seen before with rabies in raccoons and skunks (Rupprecht et al. 1995) and with bovine tuberculosis in badgers (Gallagher and Clifton-Hadley 2000). We believe that it is important to prioritize studies in mustelids on their putative role as reservoirs and amplifiers of SARS-CoV-2 infection in animals and subsequently humans. The development of appropriate surveillance and intervention strategies will determine if mustelids are one of the key links in the chain to the initiation of an unprecedented epochal event: a panzootic.

In addition to the risk of a SARS-CoV-2 reservoir becoming established in farmed mink, there is a risk of SARS-CoV-2 becoming established in wild/feral mink or other wild animals. Manes et al. (2020) warns:

Among these susceptible animals, minks are the only species farmed on a large scale in many countries that have transmitted SARS-CoV-2 to humans, suggesting their potential to become a new reservoir of SARS-CoV-2... actions are urgently needed to prevent farmed minks from becoming a reservoir of SARS-CoV-2.

In countries where fur farms operate, mink frequently escape into the surrounding environment. Around one fifth (18%) of free-ranging American mink in Ontario, Canada, have been identified as either escaped animals from fur farms or hybrids between escaped and wild animals. Despite regulations requiring fencing and traps around farms, around a quarter of mink caught by hunters in the wild in Denmark are farm-born. Boklund et al. (2021) report that holes were observed in the fencing at 15% of SARS-CoV-2 infected mink farms in Denmark and approximately 20% of farms had trees and/or bushes by which the fence could potentially be by-passed by mink or similar-sized animals. Harrington et al. (2021) state:

Mink farms are porous, and feral populations exist in almost all countries where mink are currently farmed or have previously been farmed.
Mink do not even need to escape from farms in order to transmit infection to wild and feral animals (see Section 9). In their report on SARS-CoV-2 infection in mustelids, The European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC) note that:

Farmed mink are generally farmed in open housing systems. [This] situation may allow close contact between caged mink and other animals approaching these facilities, which, if they are susceptible, may acquire SARS-CoV-2 if mink are infected.

There is evidence that fur farms can act as a source of transmission of other diseases to wild and feral mink, such as Aleutian disease virus in Canada. A joint risk assessment by the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) concluded that there is a high risk of transmission of SARS-CoV-2 from fur farms to susceptible wildlife populations in Europe. The risk assessment states:

Transmission of SARS-CoV-2 from fur farmed animals to wildlife is possible through direct contact between wildlife and infected farmed animals, as well as through indirect contact with contaminated carcasses, waste, and other fomites. Direct and indirect contact between fur farmed animals or fomites and stray animals (i.e. stray cats) is known to occur. Such stray animals could act as a bridge species by then transmitting the virus to wild susceptible species. Exposure of stray cats to SARS-CoV-2 in the vicinities of infected mink farms has been described, even in countries with known moderate to high biosecurity.

In the Netherlands 11 out of 99 cats on the infected mink farms tested positive and the virus genome sequence was similar to that in the mink. No clinical signs were observed in these cats. In addition, several dogs were found infected on the mink farms in Denmark and one in the Netherlands. Consequently, the risk of SARS-CoV-2 transmission between farmed and domestic animals on infected mink farms is high for cats and dogs.

A number of SARS-CoV-2 infections have already been detected in feral American mink in the USA and Europe. Wildlife surveillance for SARS-CoV-2 around infected mink farms in Utah, Michigan, and Wisconsin was carried out between August and October 2020. A free-ranging, wild American mink sampled in Utah was confirmed positive for SARS-CoV-2. This was the first detection of SARS-CoV-2 in a free-ranging, native wild animal from the USA. The affected animal was asymptomatic, and the virus was found to be indistinguishable from the virus characterised on a nearby affected commercial mink farm. In August 2020, 11 presumed-escaped American mink in the vicinity of infected farms in Utah tested positive for SARS-CoV-2 (11 of 11 presumed-escaped American mink tested positive; 0 of 2 presumed-wild mink tested positive). The animals exhibited high antibody titres, suggesting a potential transmission pathway to wildlife. In the vicinity of an infected farm in Oregon, 2 of 3 presumed-escaped mink tested positive.

In eastern Spain, 2 of 13 feral American mink tested positive for SARS-CoV-2. The animals were trapped as part of an invasive species trapping campaign in riverbeds in sparsely inhabited rural areas known to harbour self-sustained feral mink populations. The closest fur farm was about 20km away. This apparently represents the first example of SARS-CoV-2 acquired in the wild by feral mink in self-sustaining populations. The authors suggested that indirect transmission from humans, possibly via wastewater, may have been the source of the infections.

American mink are widespread outside their natural range, where they are invasive and can have devastating impacts on native wildlife, including prey species and other predators. If a virus reservoir is established in the wild, this poses a grave threat not only to humans but also to other wildlife species, including the critically endangered European mink (*Mustela lutreola*). A group of scientists from the UK, Spain, Estonia and Switzerland has called for large scale SARS-CoV-2 testing of wild American mink, in combination with removal trapping, across Europe, with co-ordinated action among neighbouring countries. They warn:

Although human-to-human transmission of SARS-CoV-2 is currently the dominant mechanism for the spread of COVID-19, the establishment of a wildlife reservoir could undermine efforts to combat the virus, by providing a source for re-emergence at any time and promoting conditions for the emergence and potential spread of new variants. Amongst wildlife, a disease outbreak could be devastating for the last remaining European mink populations.
Mink are largely solitary, with contact amongst adults being typically confined to the breeding season, thus limiting opportunities for onward virus transmission and persistence. However, Harrington et al. (2021) highlight several behaviours that could facilitate viral transmission in wild and feral mink, including:

- The home ranges of individuals overlap.
- Males will visit multiple females during the breeding season.
- They deposit faeces at prominent marking spots that are investigated by neighbours.
- There is widespread and sometimes extensive movement of both males and females during the autumn when the young-of-the-year disperse from their natal territory.

EFSA and ECDC note that raccoon dogs are another species of concern:

As they are susceptible and capable of shedding SARS-CoV-2, and they are bred for fur production... and are present in the wild with high abundance in Europe.

Delahay et al. (2021) caution:

The establishment of a reservoir of infection in a wild animal population would pose a significant risk to public health if it had potential to spillback into communities where the burden of infection had been reduced through control measures and/or herd immunity. Furthermore, sustained transmission in a wild host population would provide an opportunity for evolutionary adaptation of the virus, which could potentially (positively or negatively) influence transmission dynamics and the effectiveness of diagnostics and vaccines.

According to Fischhoff et al. (2021):

Back and forth transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between humans and animals will establish wild reservoirs of virus that endanger long-term efforts to control COVID-19 in people and to protect vulnerable animal populations.
Section 6: Summary

The situation in the Netherlands and Denmark during 2020 demonstrated how SARS-CoV-2 infection could spread rapidly within and between mink farms, despite enhanced biosecurity measures and surveillance, often with unidentified modes of transmission, with repeated transmission of mink-associated variants back to humans, and was only brought under control by mass culling of all mink.

The farming of mink has continued in many other countries and new outbreaks have continued to occur, creating the possibility for farmed mink to potentially become a SARS-CoV-2 reservoir (i.e. the virus could be maintained permanently in mink farms and transmitted back to humans). There is also a risk of SARS-CoV-2 becoming established in wild/feral mink and/or other wild animals. Although COVID-19 is currently spread mostly by human-to-human transmission, the establishment of a reservoir in fur farms and/or wildlife could undermine efforts to combat the virus, by providing a source for re-emergence at any time and potentially promoting the emergence and spread of new variants.

In countries where fur farms operate, mink frequently escape into the surrounding environment. A number of SARS-CoV-2 infections have already been detected in feral American mink in the USA and Europe. The typical open-sided design of fur farms facilitates contact with wild and feral animals. If a virus reservoir is established in the wild, this poses a grave threat not only to humans but also to other wildlife species, including the critically endangered European mink (Mustela lutreola).
SECTION 7: Fur-farmed species could act as ‘mixing vessels’ for human, avian and swine influenza viruses, promoting the emergence of new pandemic viruses

Influenza A viruses are prone to genetic changes that can affect pathogenicity (ability to cause disease), virulence (disease severity), and host specificity (which host species can be infected). The cyclic occurrence of influenza A epidemics and pandemics is related to the ability of the virus to modify its two main surface proteins, haemagglutinin (HA) (which allows the virus to adhere to epithelial cells in the upper respiratory tract) and neuraminidase (NA), both of which play an important role in the pathogenesis of the disease. Antigenic variability (changes in the surface proteins and carbohydrates that are recognised by the immune system) of influenza A virus may occur as antigenic drifts (minor variability) or antigenic shifts (major variability). Antigenic drifts (such as nucleotide substitutions, deletions and insertions of HA and NA genes) are responsible for seasonal influenza epidemics, while antigenic shifts cause pandemics.\textsuperscript{101}

Influenza is a segmented virus that allows for gene reassortment, where two viruses that infect the same host cell can create progeny viruses with gene segments from both parents. Genetic reassortment provides opportunities for major changes in a virus (antigenic shift) including the ability to infect and transmit in a new host. When the reassortment includes the HA gene of different subtypes, it creates the possibility of a new virus that is immunologically new to the host population, creating a potential pandemic situation. The most important changes are due to the reassortment of viruses of swine and/or avian origin with viruses of human origin, like those responsible for the pandemics that occurred in 1918 (H1N1 ‘Spanish flu’), 1957 (H2N2 ‘Asian flu’), 1968 (H3N2 ‘Hong Kong flu’), and 2009 (H1N1/pdm ‘Swine flu’).\textsuperscript{101}

Animal species that are susceptible to co-infection with human and animal influenza viruses can act as ‘mixing vessels’ in which novel reassortment viruses can be generated with the potential to cause pandemics. Receptor specificity of the HA is a major factor in determining the host range of influenza viruses. In general, avian influenza viruses preferentially recognise SA α-2,3-Gal receptors, whereas human influenza viruses preferentially recognise SA α-2,6-Gal receptors.\textsuperscript{102} Both types of receptor are found in the main species farmed for fur, including mink,\textsuperscript{103} arctic foxes,\textsuperscript{104} and raccoon dogs,\textsuperscript{104} allowing all of these species to potentially serve as intermediate hosts for influenza viruses with pandemic potential. Sun \textit{et al.} (2021) state:\textsuperscript{103}

\begin{quotation}
_{receptors} SA α-2,3-Gal and SA α-2,6-Gal are both found in the respiratory tracts of mink.
\end{quotation}

Qian \textit{et al.} 2021 conclude:\textsuperscript{104}

\begin{quotation}
Due to the co-expression of SA α-2,6-Gal and SA α-2,3-Gal receptors in a wide range of tissues, raccoon dogs and arctic foxes can potentially be infected by different IAV [Influenza A virus] subtypes, serving as potential ‘mixing vessels’ for IAVs.
\end{quotation}
A species of mammalian host may have the tendency to become a mixing vessel or natural reservoir for human or other mammalian influenza viruses if they can be infected with a large number of influenza A subtypes, particularly avian influenza subtypes. Pigs have long been recognised as a mixing vessel for reassortment of influenza viruses. Zhao et al. (2019) studied the species of mammalian hosts infected with influenza A viruses that had the highest richness, diversity, and evenness of subtypes, in order to identify species with the highest likelihood of operating as intermediate hosts for the generation of human pandemic viruses. Although isolates from pigs were found to be abundant, the subtypes were mostly mammalian influenza viruses (H1, H2, N1 and N2 accounted for the overwhelming majority). Mink were found to be infected by more influenza subtypes, including both mammalian (H3N2 and H1N1) and avian (HSN1, H9N2 and H10N4) strains and had considerably higher diversity indices. 14 HA and 13 NA sequences were found to be established from mink, of which nine pairs of HA and NA were of the typical avian strains, including two H10N4, three H5N1 and four H9N2, giving mink the highest diversity, richness and evenness of influenza subtypes. The authors conclude:

[Mink] may be both a mixing vessel and natural reservoir for IAVs

The first report of an influenza outbreak in mink was from Swedish mink farms in 1984, which was caused by influenza A H10N4 of avian origin and closely related to concomitantly circulating avian influenza virus. In recent years, there has been a steady stream of symptomatic influenza outbreaks reported in mink, and also in foxes and raccoon dogs, on fur farms in Europe, North America and China (see Table 7.1). Multiple influenza A subtypes have been identified in these outbreaks, including viruses of avian, swine and human origin and reassortment viruses. A number of cases of symptomatic influenza A virus infection have also been reported in mink, foxes and raccoon dogs in the wild (see Table 7.1).
Table 7.1.
Overview of outbreaks of human, avian and swine influenza viruses identified in species farmed for fur.

<table>
<thead>
<tr>
<th>When?</th>
<th>Where?</th>
<th>Influenza subtype(s)</th>
<th>Clinical signs</th>
<th>Possible sources identified</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2022</td>
<td>Mink farm in A Coruña, Spain.</td>
<td>Influenza A H5N1 highly pathogenic avian subtype.</td>
<td>Respiratory symptoms and increased mortality.</td>
<td>H5N1 was recently detected in domestic and wild birds in Spain.</td>
<td>Poultry-med 2022\textsuperscript{108}</td>
</tr>
<tr>
<td>2021</td>
<td>Wild red foxes in the Netherlands.</td>
<td>Influenza A H5N1 highly pathogenic avian subtype.</td>
<td>Two fox cubs showed neurological signs including seizures (one died and one was euthanized).</td>
<td>The virus was highly related to H5N1 virus identified in dead birds in the area.</td>
<td>Rijks \textit{et al.} 2021\textsuperscript{109}</td>
</tr>
<tr>
<td>2019</td>
<td>Mink farm in Utah, USA.</td>
<td>Influenza A H1N1/ pdm (2009 ‘swine flu’ human pandemic subtype).</td>
<td>Moderate to severe interstitial pneumonia and 10% mortality in kits. Minimal to moderate broncho-interstitial pneumonia with no clinical signs or deaths in adults.</td>
<td>Not confirmed but thought to be reverse zoonosis (infection from humans).</td>
<td>Clayton \textit{et al.} 2022\textsuperscript{110}</td>
</tr>
<tr>
<td>2017</td>
<td>Mink farm in Rizhao, Shandong province, China.</td>
<td>Influenza A H1N1 swine-origin triple-reassortment virus / co-infection with canine distemper virus.</td>
<td>Cough, nasal discharge, fever, lack of appetite, ataxia, cage biting, and bleeding from the mouth and nose, with mortality of 55.7% (128 of 230).</td>
<td>Not confirmed but the influenza virus was most likely acquired from pigs. The mink farm was adjacent to a pig farm and the operators did not take any precautions for the prevention and control of infectious diseases. Poultry and pig by-products in mink feed and contact with wild birds/rodents were also identified as possible sources of disease transmission.</td>
<td>Liu \textit{et al.} 2020\textsuperscript{111}</td>
</tr>
<tr>
<td>2016</td>
<td>Four unconnected raccoon dog / arctic fox farms in different areas (&gt;60km apart) of east-central Shandong province, China.</td>
<td>Influenza A H9N2 low pathogenic avian subtype with some genes derived from H7N9, suggesting that the eight isolates tested were reassortment viruses.</td>
<td>Mild respiratory symptoms including sneezing, nasal discharge, conjunctivitis and mild coughing (no deaths).</td>
<td>Not confirmed but likely to be from feed containing uncooked poultry meat by-products.</td>
<td>Qian \textit{et al.} 2021\textsuperscript{104}</td>
</tr>
<tr>
<td>When?</td>
<td>Where?</td>
<td>Influenza subtype(s)</td>
<td>Clinical signs</td>
<td>Possible sources identified</td>
<td>Reference</td>
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<tr>
<td>2015</td>
<td>Two mink farms in eastern China.</td>
<td>Influenza A H5N1 highly pathogenic avian subtype G15 (clade 2.3.2.1b) and XB15 (clade 2.3.2.1e).</td>
<td>Neurological signs, trachea haemorrhage, lung hyperaemia/haemorrhage, meningeal congestion/haemorrhage, and high mortality (55.7% at one farm and 64.4% at the other farm).</td>
<td>Not confirmed but could have been from wild birds or from incompletely treated chicken and duck meat in mink feed.</td>
<td>Jiang et al. 2017112</td>
</tr>
<tr>
<td>2013</td>
<td>Mink farm in mideastern Shandong province, China.</td>
<td>Influenza A H9N2 avian subtype.</td>
<td>Mild respiratory distress, conjunctivitis, sneezing, nasal discharge, mild coughing (no mortality).</td>
<td>Not confirmed but likely to be from uncooked poultry meat by-products in feed.</td>
<td>Peng et al. 2015113</td>
</tr>
<tr>
<td>2011</td>
<td>Mink farm near Stavanger in southwestern Norway.</td>
<td>Influenza A H1N1/pdm (2009 ‘swine flu’ human pandemic subtype).</td>
<td>Adult mink had nasal discharge and some coughing and sneezing. Increased mortality in kits (approx. 1000 kits died in the month following the first observed respiratory signs compared with expected kit mortality of about 200 animals).</td>
<td>The virus most closely resembled viruses circulating in humans in Norway during the 2010-2011 winter season. No clinical signs were reported in farm workers but it could have been transmitted from sub-clinically infected humans. Alternatively, since human viruses were the likely source of earlier outbreaks of H1N1 in Norwegian pigs, the genetic data are also consistent with infection via feed containing virus from infected pigs (mink feed included frozen pig offal).</td>
<td>Akerstedt et al. 2012114</td>
</tr>
<tr>
<td>2011</td>
<td>Three mink farms in the Netherlands (two in the south and one in the west).</td>
<td>Influenza A H1N1/pdm (2009 ‘swine flu’ human pandemic subtype).</td>
<td>Interstitial pneumonitis and increased mortality of kits (11-30%). All kits with clinical signs died.</td>
<td>Influenza-like symptoms were reported in farm workers. One farm reported that the disease appeared to spread from one corner of the farm where there were many wild birds.</td>
<td>Willigen and Dijkman 2012115</td>
</tr>
<tr>
<td>2010</td>
<td>Mink farm in Midwest USA.</td>
<td>Influenza A swine-origin H1N2 / co-infection with haemolytic Escherichia coli.</td>
<td>Severe cough, lethargy, mucoid/watery discharge from eyes, persistent severe respiratory distress and nose/mouth bleeding.</td>
<td>Not confirmed but the source appeared to be uncooked turkey meat in the mink feed because cross-species transmission of swine influenza viruses (particularly H1N2 and H3N2) to turkeys commonly occurs.</td>
<td>Yoon et al. 2012116</td>
</tr>
<tr>
<td>When?</td>
<td>Where?</td>
<td>Influenza subtype(s)</td>
<td>Clinical signs</td>
<td>Possible sources identified</td>
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<tr>
<td>2010</td>
<td>Mink farm in Nova Scotia, Canada.</td>
<td>Influenza A H3N2 and H1N1/pdm (2009 ‘swine flu’ human pandemic subtype) reassortment virus.</td>
<td>Severe coughing but low mortality in mink kits.</td>
<td>Not determined but possibly via pig meat in mink feed because a similar reassortment virus was identified in swine in Quebec.</td>
<td>Tremblay et al. 2011</td>
</tr>
<tr>
<td>2009-2010</td>
<td>18 mink farms in 2009 and 4 mink farms in 2010 in Denmark.</td>
<td>2009 outbreak: Influenza A H3N2, probably originating from circulating swine influenza. 2010 outbreak: H1N1/pdm (2009 ‘swine flu’ human pandemic subtype).</td>
<td>Sneezing, coughing and bleeding from the nose.</td>
<td>Affected farms had a common feed supplier and the most plausible transmission route was from raw untreated pig waste containing lungs used in the production of mink feed. The first clinical symptoms were observed a few weeks after the raw pig waste was added to the mink feed.</td>
<td>Larsen et al. 2012</td>
</tr>
<tr>
<td>2006-2007</td>
<td>Multiple mink farms in Nova Scotia, Canada.</td>
<td>Influenza A H3N2 genetically related to (but antigenically distinct from) a triple reassortment influenza virus that emerged in Canadian swine in 2005.</td>
<td>Respiratory problems / pneumonia / increased mortality.</td>
<td>All of the mink were fed a ration including uncooked meat by-products of pigs, beef and poultry, including ground swine lung purchased in frozen blocks from areas of the country where swine influenza H3N2 was prevalent.</td>
<td>Gagnon et al. 2009</td>
</tr>
<tr>
<td>2006</td>
<td>Wild mink in Oskarshamn, Sweden.</td>
<td>Influenza A H5N1 highly pathogenic avian subtype.</td>
<td>The mink was found dead.</td>
<td>The virus was also identified in wild birds found dead in the area.</td>
<td>Kiss et al. 2008</td>
</tr>
<tr>
<td>2005</td>
<td>Raccoon dog farm in Shandong province, eastern China.</td>
<td>Influenza A H5N1 highly pathogenic avian subtype.</td>
<td>Approx. 100 raccoon dogs (out of 1000 on the farm) died from respiratory disease and/or diarrhoea in January 2005.</td>
<td>Not determined but assumed to be from chicken carcasses used in feed.</td>
<td>Qi et al. 2009</td>
</tr>
</tbody>
</table>
Influenza infections in fur-farmed species may occur with minimal or no clinical signs. Influenza in mink, foxes and raccoon dogs is not a notifiable disease and there is a lack of systematic surveillance of influenza viruses on fur farms. Reports of symptomatic influenza outbreaks on fur farms (see Table 7.1) are therefore likely to represent only the tip of the iceberg. Where widescale testing of asymptomatic mink on fur farms has been carried out, the findings indicate that farmed mink are commonly infected with multiple strains of human and avian influenza viruses.

Following reports of interstitial pneumonitis and increased mortality of kits on three mink farms in the Netherlands in 2011 (see Table 7.1), which was attributed to influenza A H1N1/pdm (2009 ‘swine flu’ human pandemic subtype), wider testing was carried out. In total, testing for influenza antibodies was performed on 25 mink farms and 72% were positive, with 60% of these farms having no clinical symptoms in kits.

In 2013, 560 sera were collected from mink farms in five different areas of Shandong province, China (which produces more than 50% of the mink in China) and tested for antibodies to influenza A H9N2, H5N1 and H7N9 subtypes. Samples were collected from 114 adult mink and 446 young mink showing no obvious signs of disease. 45.4% and 47.5% of samples were positive for antibodies to two different H9N2 strains respectively. 1.8% and 6.4% were positive for antibodies to two different H5N1 strains respectively. No antibodies to H7N9 were detected.

In 2015, also in Shandong, 313 mink serum samples from 7 farms, 256 raccoon dog serum samples from 5 farms, and 128 fox serum samples from 4 farms were tested for anti-H9 antibodies. 31.0% of the mink samples, 41.4% of the raccoon dog samples, and 59.4% of the fox samples were positive for antibodies to H9.

Between September 2016 and March 2019, a total of 2,455 blood samples were collected from 34 mink farms in northern China (1,772 from Shandong province and 683 from Hebei province). The samples were tested for antibodies to prevalent human (H1N1/pdm and H3N2) and avian (H5N6, H7N9 and H9N2) influenza viruses. The overall seroprevalence of human and avian influenza viruses in the collected mink samples was 76.8%, of which 47.3% were positive for H1N1/pdm, 11.4% for H3N2, 39.7% for H9N2, 3.9% for H7N9, and 2.8% for H5N6. Co-infection with avian and human influenza subtypes was found to be common in mink. 34.7% of the samples were seropositive for multiple influenza subtypes, of which 32.3% contained both avian and human influenza antibodies. Correlational analysis indicated that transmission of human influenza viruses occurred from humans to mink, and that feed source was a probable route of avian influenza virus transmission to farmed mink. Infection and transmission experiments showed that mink were susceptible and permissive to circulating avian and human influenza viruses, and that human influenza viruses (H3N2 and H1N1/pdm), but not avian viruses, were capable of aerosol transmission among mink. Sun et al. (2021) conclude:

These results indicate that farmed mink could be highly permissive ‘mixing vessels’ for the reassortment of circulating human and avian influenza viruses.

Liu et al. (2020) note that a lack of obvious clinical symptoms or the presence of only mild signs of infection, such as coughs and running noses, when mink are infected with low pathogenic influenza strains such as H9N2 or H1N1/pdm, do not attract the attention of farmers. Influenza viruses are therefore allowed to persist on mink farms for extended periods, giving the opportunity for these viruses to survive and adapt in mink, potentially leading to novel subtypes with increased host ranges.
A mutation associated with adaptation to mammals has been reported in a H9N2 avian influenza virus isolated from mink on a Chinese farm in 2014. Xue et al. (2017) conclude that circulation of H9N2 in mink may drive the virus to adapt to mammals and warn:  

...the mink farm might be an ideal place that the avian influenza virus adapts to mammalian species.

Studies have shown that when the H7N9 highly pathogenic influenza viruses replicate in ferrets or humans, they easily acquire certain mammalian-adapting mutations and become highly lethal in mice and highly transmissible in ferrets by respiratory droplet, creating the potential for human-to-human transmission.

The possibility of a human pandemic caused by a highly pathogenic H5N1 avian influenza virus is of particular concern because of the severity of disease associated with this subtype. Since 2003 up to 31 March 2022, a total of 864 human cases of H5N1 infection, and 456 deaths, have been reported worldwide from 18 countries. While the H5N1 virus transmits zoonotically from infected poultry to humans, often with fatal consequences, such transmission is inefficient. Although the virus replicates efficiently in diseased humans, it has not yet adapted to efficient human-to-human transmission.

Two H5N1 highly pathogenic avian influenza viruses isolated from mink in eastern China in 2015 (named G15 and XB15) were found to have undergone substantial antigenic drift, resulting in reduced protection in chickens vaccinated with the Re-6 vaccine used against H5N1 in poultry. The new strains also appeared to have gained virulence in mammals, showing efficient replication and moderate to high pathogenicity in mice without pre-adaptation. Jiang et al. (2017) conclude:

...continued circulation of the G15 and XB15 viruses poses a significant threat to livestock, and in particular commercial poultry, as well as human beings.

Reperant et al. (2008) demonstrated that red foxes fed infected bird carcasses can become infected with highly pathogenic H5N1 avian influenza and can excrete virus while remaining free of severe disease, thereby potentially playing a role in virus dispersal.

Potential sources of influenza infection in fur farms include raw or incompletely treated feed (especially containing poultry and/or pig meat by-products), contact with infected wild birds and/or other wildlife, and contact with infected farm workers (see Table 7.1). Many studies link infection in fur-farmed animals with contaminated feed. Feeding of raw untreated poultry and pig meat by-products to animals on fur farms is very common. In some cases, meat by-products may be frozen prior to inclusion in feed but there have been influenza outbreaks on fur farms associated with the use of frozen pig lungs so this may not prevent transmission. One study in Denmark reported that poultry ingredients in mink feed were heat-treated, while pork by-products were frozen. No influenza viruses were detected in the final product but the authors note that it may be quite difficult to detect influenza viruses in feed as viruses do not multiply in the feed in the way that bacteria do and only small samples of the feed were tested. The ready-to-eat mink feed was, however, found to contain a cocktail of mycotoxins and bacteria. Sun et al. (2021) conclude:

...to reduce the risk of emergence of novel pandemic viruses, feeding mink with raw poultry by-products should not be permitted, and epidemiological surveillance of influenza viruses in mink farms should be urgently implemented.

However, replacing raw poultry by-products in fur animal feed would be challenging because the cooking process may negatively impact the absorption of essential metabolites such as amino acids and fats. The introduction of high amounts of cooked poultry offal in mink feed has been associated with health problems in growing mink, including impaired growth and kidney damage.
Section 7: Summary

Animal species that are susceptible to co-infection with human and animal influenza A viruses can act as ‘mixing vessels’ in which novel reassortment viruses can be generated with the potential to cause pandemics.

Mink, arctic foxes and raccoon dogs possess cell receptors that make them susceptible to infection with both human and avian influenza A viruses. Influenza infections in fur-farmed species may occur with minimal or no clinical signs. Influenza in mink, foxes and raccoon dogs is not a notifiable disease and there is a lack of systematic surveillance of influenza viruses on fur farms. Reports of symptomatic influenza outbreaks on fur farms are therefore likely to represent only the tip of the iceberg. Where widescale testing of asymptomatic mink on fur farms has been carried out, farmed mink have been found to be commonly infected with multiple strains of human and avian influenza viruses. This indicates that farmed mink could be highly permissive ‘mixing vessels’ for the reassortment of circulating human and avian influenza viruses.

Potential sources of influenza infection in fur farms include raw or incompletely treated feed (especially containing poultry and/or pig meat by-products), contact with infected wild birds and/or other wildlife, and contact with infected farm workers.
SECTION 8:
Fur farms provide the ideal conditions for the spread of SARS-CoV-2 and influenza A viruses and the emergence of new variants

The large numbers of animals kept in crowded and chronically stressful conditions in fur farms create the perfect breeding ground for disease, including zoonotic disease. Diaz et al. (2021) state:20

Overcrowded housing conditions inherent within intensive mink farms, often combined with poor sanitation and welfare, both guarantee spread of SARS-CoV-2 and facilitate opportunities for viral variants, thereby effectively representing biotic hubs for viral transmission and evolution of virulence.

According to Fenollar et al. (2021):132

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).

In their report on SARS-CoV-2 infection in mustelids, The European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC) note:88

...large mink farms with high animal density provide ideal conditions for SARS-CoV-2 replication and transmission.

In relation to influenza A viruses, Kessler et al. (2021) state:133

Usually, minks are kept in small cages right next to each other in holdings with up to 10,000 animals, facilitating aerogenic viral spread... the high diversity of IAV subtypes and their co-circulation in minks could give rise to new reassortment viruses with zoonotic potential.
To summarise, fur farms provide the ideal conditions to promote the spread of SARS-CoV-2 and influenza A viruses and the emergence of new viral variants due to:

- **High density of animals**: typically thousands or tens of thousands per farm, housed in close confinement in adjacent cages.88
- **High density of farms**: fur farms are often geographically concentrated.134
- **Chronically stressful housing conditions**: potentially leading to immunosuppression.135
- **Low genetic diversity** of the animals.132
- **Poor sanitation**: fur farms typically lack sophisticated manure handling systems – urine and faeces drop from the cages to the slurry gutter or to the floor of the house, where they are stored for days or weeks.137
- **Poor biosecurity**: fur farms typically use open-sided housing, which facilitates contact with wild/feral animals, fur-farmed animals frequently escape into the surrounding environment (see Section 6 and Section 9), and fur animal feed can contain a cocktail of potentially pathogenic microorganisms (see Section 7).
- **Use of highly susceptible animal species**: fur-farmed species are highly susceptible to SARS-CoV-2 (see Section 3) with the potential to form a permanent reservoir of SARS-CoV-2 infection (see Section 6) and are also susceptible to co-infection with a high diversity of human, avian and swine influenza A viruses, with the potential to act as 'mixing vessels', providing opportunities for reassortment into new viruses with pandemic potential (see Section 7).
- **Exposure to a high diversity of viruses**: animals on fur farms are exposed to human viruses from farm workers and to a high diversity of animal viruses through contact with wild/feral animals and the feeding of raw or inadequately treated animal products from multiple species, including poultry and pigs, in which influenza A viruses with the potential for reassortment into new viruses with pandemic potential are known to circulate (see Section 7).
- **Lack of systematic surveillance** of circulating influenza viruses in fur farms.119

The combination of factors listed here makes fur farms uniquely risky for public health, both within the context of the current COVID-19 pandemic, and in terms of the potential to facilitate the emergence of future pandemics. These factors include high animal density within farms, geographical concentration of farms, chronically stressful housing conditions, low genetic diversity, poor sanitation, poor biosecurity, use of species highly susceptible to infection with both SARS-CoV-2 and multiple human, avian and swine influenza A viruses, exposure to a high diversity of human and animal viruses, and a lack of systematic surveillance of circulating viruses.

Indeed, it is hard to imagine how the fur industry could provide more ideal conditions for the emergence and spread of new viruses with pandemic potential.
SECTION 9:
Biosecurity, surveillance and vaccination programmes are not sufficient to address the public health risk from fur farms

According to the World Animal Health Organisation (OIE): 30

Biosecurity means a set of management and physical measures designed to reduce the risk of introduction, establishment and spread of animal diseases, infections or infestations to, from and within an animal population. In broad terms, it refers to anything designed to prevent the transfer of disease causing pathogens.

The open-sided housing system typically used on fur farms makes it impossible to achieve a high level of biosecurity. This housing design facilitates contact with wild birds and other wild and feral animals (see Section 6). Even if closed housing systems were to be adopted, an exchange of pathogens with the environment can never be fully prevented. 133

Seagulls, most often herring gulls, are frequently observed on Danish mink farms, from a few individuals to flocks of up to 80 birds (and occasionally up to 500 birds have been observed). 44 One Danish herring gull frequently visited four mink farms within a distance of 3-4km from its breeding ground during a two year observation period, including 57 days when more than one mink farm was visited on the same day. 44 The mink feed attracts the gulls, especially at feeding time, and the birds can easily gain access to open-sided houses to forage around the mink cages. 44 While large birds such as seagulls are usually seen on the roof of fur-farm buildings, or feeding beneath the cages, smaller birds can be observed feeding on top of the cages. 44 The presence of wild birds around cages on fur farms is clearly a concern for the potential transmission of avian influenza viruses. Birds are not generally susceptible to SARS-CoV-2, however the finding of SARS-CoV-2 on the foot of a seagull at a farm in Denmark suggests that they could act as mechanical vectors, potentially carrying virus from one farm to another. 44 Seagulls or other birds were described as a burden by farmers on almost 70% of SARS-CoV-2 infected mink farms in Denmark. 44

Bats may roost in fur farm buildings and are host to many viruses, especially coronaviruses. The attractive effect of anthropized environments on bats with differing biological needs results in a higher concentration and biodiversity of bat-borne viruses. 138 This increases the risk of transmission of viruses through direct contact or contamination by urine or faeces. 138

It is likely that rodents can act as a mechanical vector of avian influenza viruses. 130 Wild rodents can also be infected with several influenza viruses of avian origin, and replication is possible without prior adaptation of the virus to rodents, so it is possible that rodents may shed virus in nasal excreta and saliva and also contaminate the environment with their excreta, which may contain sufficient amounts of virus to facilitate transmission. 139

Several studies suggest that flies could act as a mechanical vector of both SARS-CoV-2 140 and highly pathogenic H5N1 avian influenza virus. 141 142 143 SARS-CoV-2 was detected on flies on infected farms in Denmark. 44 Local residents frequently report problems with flies in the vicinity of fur farms. 144 145 146 The typical use of open-sided houses on fur farms, with manure stored for days or weeks at a time in the slurry gutter or on the floor beneath the cages, 137 provides the perfect breeding ground for flies. Most feed used on fur farms is wet and high in protein, which is also ideal substrate for fly larval development. 147

The pelts of the animals are another potential source of virus transmission. Virtanen et al. (2021) 148 tested the survival of SARS-CoV-2 on various clothing materials and found that the virus could be cultured from mink fur even after 10 days (and since no time points beyond that were tested, some virus particles might have stayed infectious even longer). The authors conclude:

SARS-CoV-2 stability on tested clothing materials varied from minutes on cotton to [10] days on pelts, and precautions need to be taken especially when handling fur animals and their pelts due to the long survival time of the virus.
They also noted that inactivation of the virus was more challenging on fur:

> Based on our results, UV-C light treatment is not suitable to inactivate the virus on fur due to the mechanical protection of the fur. Heat treatment in dry heat completely inactivated the virus on all materials, but inactivation on mink pelt in water bath was insufficient.

OIE guidance on working with farmed animals of species susceptible to infection with SARS-CoV-2 states:

> The following precautions are recommended to avoid introduction and/or transmission of SARS-CoV-2 to farmed animals of moderate to highly susceptible species by pests and roaming animals: Exclude all domestic animals (dogs, cats, etc.), as well as rodents, birds, and other wildlife from farm buildings, ensuring that the facilities are as pest-proof as possible.

Excluding birds, rodents and other wildlife and feral animals from buildings when the buildings typically do not have external walls is clearly not going to be feasible. The best fur farms might be able to achieve is to erect fencing/netting around farms and install traps but these measures have already been shown to be inadequate to prevent the escape of mink from farms, since this is still a common occurrence in areas where farms have implemented these measures (see Section 6). Unsurprisingly, Domanska-Blicharz et al. (2021) note:149

> The implemented biosecurity procedures on mink farms in most affected countries (especially in the Netherlands and Denmark) turned out to be insufficient, infections in mink have spread on a large scale, and the occurrence of SARS-CoV-2 in people connected to mink farms has also increased.

Similarly, Diaz et al. (2021) note:20

For highly pathogenic avian influenza, domestic poultry are the main viral reservoir.¹⁵⁰,¹⁵¹ Therefore, improving the biosecurity of fur farm buildings would be expected to have little impact on reducing the introduction of these viruses to fur farms when the animals are fed large quantities of raw or inadequately treated poultry by-products (see Section 7).

A number of countries have started vaccinating mink against SARS-CoV-2, including Russia,¹⁵² USA,¹⁵³ and Finland.¹⁵⁴ There is currently limited information published on the effectiveness of these vaccines. The first SARS-CoV-2 vaccine for animals was reportedly developed in Russia. A news report states that it is an inactivated vaccine for carnivores that elicited antibody production in 100% of tested animals, however:¹⁵⁵

> ...the precise length of immunity is not yet known, and the observation of tested animals continues. At this point, we can definitely say at least six months. But it is unlikely to last much longer. This is the nature of inactivated vaccines, which are usually given annually.

It was not reported whether vaccinated animals were challenged with viral exposure or whether the vaccine affects transmission. The presence of antibodies does not necessarily translate to protection from infection and prevention of transmission. For example, there is evidence that mink can be re-infected with SARS-CoV-2 following recovery from an initial infection.¹⁹ Mink on a farm with about 15,000 animals in Denmark became infected with SARS-CoV-2 (75% tested positive for SARS-CoV-2 RNA in throat swabs and 100% of animals were seropositive). The mink showed few signs of disease and only low mortality and were allowed to recover from the infection. Follow-up studies demonstrated the absence of infection but maintenance of antibodies against the virus. However, after a period of more than two months without any virus detection, over 75% of tested animals were again found to be positive for SARS-CoV-2 RNA.¹¹ The viruses responsible for the second wave were slightly different from those found in the first wave but were closer to each other than to the viruses found on other mink farms. Antibody levels in mink during the second wave of infection were much higher than during the initial round of infection but were still insufficient to confer protection against re-infection. The authors note:¹¹

> ...the mink did exhibit a boost in antibody levels following the re-infection, suggesting the immune response to the initial infection was inadequate to block virus replication. Currently, there are no ‘correlates of protection’ that can be used to evaluate the immune responses in mink.
Therefore, even if mink show a good antibody response to vaccination, it does not necessarily guarantee that SARS-CoV-2 will not continue to circulate in mink. Shuai et al. (2021)\textsuperscript{92} found that two doses of a spike protein-based subunit vaccine largely prevented SARS-CoV-2 replication and lung damage in mink following virus challenge five weeks after the second vaccination. However, protection may not be complete because some infectious virus was detected in nasal washes from one of three vaccinated mink tested on day 2 post challenge (infectious virus was detected in the nasal washes of three control mink on days 2, 4, 6 and 8 post challenge) and it is not known how long protection was maintained beyond five weeks.

Investigations of antibody production and responses to infection in mink vaccinated against SARS-CoV-2 in Finland have produced unpromising results.\textsuperscript{156} In vitro tests indicated that the neutralising antibodies from vaccinated mink could protect cell lines against early 2020 dominant variants (Wuhan and Alpha) but poorly against later dominant strains (Beta and Delta). Antibodies could be detected in sera samples of vaccinated mink for at least 23 weeks after receiving two doses of the vaccine. However, although monitoring of clinical signs suggested that the vaccine reduced disease severity in the mink, it was ineffective in preventing infection:\textsuperscript{156}

The presence of the virus was monitored in collected saliva samples throughout the infection days to study the effect of the vaccine on preventing the mink from SARS-CoV-2 infection by reverse transcription (RT) PCR. The quantification cycles (Cq) values were similar between vaccinated and non-vaccinated mink of both genders and between different gender, indicating that the vaccine could not help with preventing SARS-CoV-2 infection.

Experience with COVID-19 vaccines in humans indicates that vaccination does not necessarily prevent infection or transmission, and waning effectiveness has necessitated multiple booster doses.\textsuperscript{157} It is unclear how much protection would be given by annual vaccinations in mink. Also, vaccines are likely to be given to breeding animals only\textsuperscript{154} and it is not clear whether any protection would be conferred on kits.

The use of vaccination against influenza viruses on fur farms would also be problematic. Kessler et al. (2021) state:\textsuperscript{133}

Kong et al. (2015) report disappointing results with an inactivated vaccine:\textsuperscript{158}

An MF59-adjuvant H7N9 inactivated vaccine is reported to be well-tolerated and immunogenic in humans, however a study in ferrets indicated that while a single dose of the inactivated H7N9 vaccine reduced disease severity, it did not prevent virus replication and transmission.

A live attenuated H7N9 vaccine did prevent transmission in guinea pigs, however:\textsuperscript{158}

The risk of reassortment of the vaccine virus with a circulating influenza virus, resulting in a novel subtype of influenza that could spread in the human population, is a noteworthy concern associated with the use of a live attenuated influenza vaccine bearing surface genes derived from a novel influenza virus subtype.

An additional concern is that vaccination of fur animals would make it harder to detect actual infections in fur farms, due to the challenges of distinguishing antibody responses to vaccination from those to actual infection. Sun et al. (2021)\textsuperscript{103} note that it is currently relatively straightforward to perform sero-surveillance for influenza virus infections in mink because the animals are not vaccinated against influenza viruses.

A number of intervention steps have been suggested to try to reduce the public health risk from fur farms in relation to influenza, including:\textsuperscript{103}

\begin{itemize}
  \item A ban on the use of raw animal products in feed (although this would likely be problematic due to negative effects on the health of the animals -- see Section 7).
  \item Urgent implementation of regular virus surveillance on fur farms.
  \item Isolation of all fur farm workers with respiratory symptoms.
\end{itemize}

However, the public health risk associated with fur farms is largely inherent in the species and the farming system used. Therefore, the farming of animals for fur poses an unacceptable public health risk that cannot be adequately mitigated. Given the non-essential nature of the product, it is hard to see how this risk can be justified.

Inactivated [influenza A] vaccines often do not induce efficient cross reactivity and thus, are only efficient for the particular matching strain. Live vaccines can be more efficient but harbor a certain risk of regaining virulence by mutation or reassortment... Even though there have been promising vaccine strategies developed, unpredictable viral evolution remains the biggest challenge.
Section 9: Summary

The open-sided housing system typically used on fur farms makes it impossible to achieve a high level of biosecurity. This housing design facilitates contact with wild birds and other wild and feral animals. Even if closed housing systems were to be adopted, an exchange of pathogens with the environment can never be fully prevented.

For highly pathogenic avian influenza, domestic poultry are the main viral reservoir. Therefore, improving the biosecurity of fur farm buildings would be expected to have little impact on reducing the introduction of these viruses to fur farms when the animals are fed large quantities of raw or inadequately treated poultry by-products. Replacing raw poultry by-products in fur animal feed would likely be problematic due to negative effects on the health of the animals.

Experience to date, particularly in the Netherlands and Denmark, indicates that biosecurity measures, targeted culls and active surveillance have not been sufficient to prevent widespread SARS-CoV-2 infections on fur farms and repeated transmission of mink-associated viruses to people.

It is currently unclear to what extent vaccination of animals on fur farms might be able to reduce transmission of SARS-CoV-2 and/or influenza A viruses but vaccination comes with multiple challenges and risks and is very unlikely to be able to eliminate transmission entirely. Initial findings in relation to a SARS-CoV-2 vaccine used in mink in Finland indicate that the vaccine is unable to prevent infection.

The public health risk associated with fur farms is largely inherent in the species and the farming system used. Therefore, the farming of animals for fur poses an unacceptable public health risk that cannot be adequately mitigated. Given the non-essential nature of the product, it is hard to see how this risk can be justified.
CONCLUSIONS AND RECOMMENDATION

The farming of animals for fur presents an unnecessary and unacceptable risk of exacerbating the current pandemic and potentially promoting the emergence of future pandemics of human respiratory disease.

This risk to public health is largely inherent in the species and farming system used by the fur industry and cannot therefore be adequately mitigated.

The gravity of the threat, combined with the non-essential nature of the product, brings a new urgency to the need for a complete ban on the farming of animals for fur and the sale of fur products in the European Union and across the world.
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