



# Mink Farming & SARS-CoV-2

**An Examination of the Science and Scale of  
Problems Associated with Mink Farms:**

**SARS-CoV-2 Spillover to Humans and Wildlife, Emerging New Variants,  
and Animal Welfare Problems For Mink on Intensive Farms.**

January 2022

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## **Mink farming & SARS-CoV-2**

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<b>Table of Contents</b>	<b>Page(s)</b>
<b>Review and analysis.....</b>	<b>6-13</b>
I - Executive summary.....	6
II - Underlying risk factors posed by captive mink on farms .....	6
III - Key findings .....	7
IV - Key policy conclusions and recommendations.....	9
V - Methodology.....	11
Authorship .....	11
Acknowledgments.....	11
Pictogram overview of Supplement 1 .....	12
Pictogram overview of Supplements 2 to 5.....	13
<b>Supplement 1 - Details of seven reasons why farmed mink put public health at risk from SARS-CoV-2 .....</b>	<b>14-49</b>
1. Reason #1 - Mink are hyper-susceptible to SARS-2 infection, disease & death.....	14
<i>Box 1</i> - Natural SARS-CoV-2 infections in animals as of February 2021.....	14
<i>Table 1A</i> - Global mink farm SARS-CoV-2 outbreaks - April 2020 to Nov 2021.....	15
<i>Table 1B</i> - Major nation and worldwide farmed mink pelt production (millions), 2017 to 2021 in 36 mink-rearing nations .....	16
<i>Table 2</i> - Mortality rates in mink infected by SARS-CoV-2 on 18 U.S. mink farms in four states .	17
<i>Figure 1</i> - Thirteen countries & four U.S. states with farmed mink SARS-2 outbreaks 2020-21...	18
2. Reason #2 - Mink catch SARS-2 from people (spillover) & return the favor (spillback).....	18
3. Reason #3 - Escaped, feral & wild mink are an infection reservoir for human SARS-CoV-2.....	19
<i>Figure 2</i> - Current native (North America) and introduced (Eurasia, South America) distributions of free-ranging American mink ( <i>Neovison vison</i> ).....	19
A. Peer-reviewed studies & public health reports underscore SARS-2 wildlife reservoir threat..	20
B. Media and other reports echo scientific concerns over SARS-CoV-2 in wildlife reservoirs .....	21
C. Farmed and free-ranging white-tailed deer heavily infected with SARS-CoV-2 .....	22

*Figure 3* - Short & long term US, EU & global public health risks from SARS-2 in farmed mink .23

4. Reason #4 - Are mink the “missing link” between bats and people? .....24

*Figure 4* - SARS-CoV-2 zoonotic transmission chain: bats, primates & carnivores ..... 25

5. Reason #5 - Mink SARS-CoV-2 mutants infecting people may evade vaccines or be more virulent or contagious ..... 26

A. Diversity in SARS-CoV-2: mutation and recombination ..... 26

*Figure 5* - SARS-2 spike protein binds to host angiotensin-converting enzyme 2 in lungs ..... 27

B. Mink-associated SARS-CoV-2 variants ..... 28

*Box 2* - Spillover, spillback, and the perfect public health storm in farmed mink ..... 29

*Figure 6A* - Chronology of a typical mink outbreak of SARS-2: spill-over and spill-back..... 30

*Figure 6B* - Epidemic curves for SARS-2 Cluster 5 (Y453F) receptor-binding domain mutant variant in 915 people and 290 mink farms in Denmark 2020-21 ..... 31

*Figure 6C* - Weekly and cumulative infections of SARS-2 in humans (official) and mink (estimated) from February 2020 through January 2021 ..... 33

C. The public health impact of mink SARS-CoV-2 spike protein variants ..... 34

*Table 3* - Public health relevance of mink SARS-2 variant mutants: findings from 16 studies..... 35

*Figure 7A* - Wild type and mutant virus neutralization and host-virus bond..... 36

*Figure 7B* - Reduced antibody protection against mink SARS-CoV-2 mutant RBD variants..... 36

D. Long-term impact of escape mutants: SARS-2 endemicity as series of unfortunate events .... 37

*Figure 8* - SARS-CoV-2 escape mutants and COVID-19 endemicity ..... 38

*Table 4* - Exiting the path to SARS-CoV-2 endemicity: decreasing public health risk of SARS-CoV-2 escape mutants by banning mink farming ..... 39

6. Reason #6 - Farmed mink are raised in high stress-low welfare conditions that maximize chances for dangerous SARS-CoV-2 infections and mutations ..... 39

*Box 3* - Farmed mink manual restraint ..... 41

7. Reason #7 - Vaccinating mink is not a panacea for the high volume-low welfare conditions of fur farming that makes mink so vulnerable to disease in the first place ..... 42

*Box 4* - Simple math of mink farm herd immunity and vaccine protection ... & failure..... 43

8. Agreement of our findings with January 2021 WHO/OIE/FAO report ..... 44

*Table 5* - Likelihood of three adverse and consequential outcomes from SARS-2 in farmed mink in the U.S. .... 45

*Figure 9A* - Likelihood of SARS-CoV-2 introduction and spread within mink farms in 36 fur farming nations..... 46

*Figure 9B* - Likelihood of SARS-CoV-2 spill-over from mink fur farming to humans in 36 fur-farming nations..... 46

*Figure 9C* - Likelihood of SARS-CoV-2 spread from mink fur farming to susceptible wildlife populations in 36 fur-farming nations ..... 47

9. A history lesson, a cautionary tale, and call to action against SARS-CoV-2 in farmed mink..... 47

*Figure 10A* - N American distribution of Chronic Wasting Disease in wild & captive cervids..... 49

*Figure 10B* - Farmed wildlife: high consequence pathogen spill-over and spill-back ..... 49

**Supplement 2 - Background information on wild and farmed mink and relation to COVID-19 risk ..... 50-65**

1. The wild American mink ..... 50

2. The farmed American mink ..... 50

*Box 5* - The two species of wild mink ..... 51

*Figure 11* - Yearly production life cycle of farmed mink ..... 51

*Figure 12* - Relative changes in mink farm census over an annual production cycle ..... 52

A. Susceptibility to SARS-CoV-2 and other infectious diseases ..... 53

B. SARS-CoV-2 as a mink “Disease of Production” ..... 54

C. The critical role of human contact..... 55

3. Comparison of farmed and wild American mink..... 56

*Figure 13* - Denatured conditions drive infection and transmission risk in farmed mink ..... 57

*Figure 14A1* - Phenotype comparison of wild free-living vs. farmed American mink .....58

*Figure 14A2* - Comparison of wild vs. farmed mink habitats and living space.....59

*Figure 14B* - Diets of farmed mink vs. wild mink..... 60

*Figure 14C* - Visible and invisible impacts of high stress on farmed mink ..... 61

*Figure 14D* - Denatured farmed mink ..... 62

4. The U.S. farmed mink industry ..... 63

*Figure 15* - Simple mink farm micro-economic model..... 63

*Figure 16* - U.S. mink pelt production, the average price per pelt, and farm-gate value of mink industry..... 64

*Table 6* - U.S. mink farm macro-economic comparisons: 2011 vs. 2019 vs. 2020.....65

*Table 7* - Informative web-based videos of wild mink, feral mink, and mink farms ..... 66

**Supplement 3 - Feral farmed mink as an invasive and injurious species.....67-70**

1. Definitions ..... 67

2. Escaped and feral mink as invasive ..... 67

*Box 6 - Escaped male captive-born, male wild-born & female wild-born mink in Denmark* ..... 68

3. Supporting scientific literature on injurious nature of farmed mink ..... 68

4. Summary: farmed mink are an “injurious species” harming human, animal and eco-system health ..... 69

**Supplement 4 - Mutant variants of SARS-CoV-2 from mink..... 71-86**

1. Background..... 71

2. Abbreviations & definitions..... 71

3. Methods to assess public health risk from SARS-CoV-2 variants ..... 73

*Figure 17 - Virus neutralization assay for mink variant with mutated spike protein RBD* ..... 73

4. The SARS-CoV-2 genome and proteins most relevant to mink mutant variants ..... 73

*Figure 18 - SARS-CoV-2 genome structure and two most important virus proteins* ..... 74

*Figure 19 - Six amino acid mutations in spike protein RBD common in mink-origin SARS-CoV-2 variants* ..... 75

*Figure 20 - The “Cluster 5” mink-associated mutations in the SARS-CoV-2 spike protein* ..... 76

5. Risky mink spike protein N501T mutation ..... 77

6. Review of scientific literature on public health risks from mink variants of SARS-CoV-2..... 77

*Table 8 - Seventeen studies that examined mink-origin SARS-CoV-2 mutant variants* ..... 77-79

*Tables 9A - 9G - Details of 17 studies of mink SARS-CoV-2 mutant variants* ..... 80-86

**Supplement 5 - Cited references & image credits ..... 87-104**

*Table 10 - References cited by information source* .....87

    References ..... 87-100

*Table 11 - Credit for and sources of images* ..... 101-104

## ***Review and analysis***

### ***I - Executive summary***

This updated (January 2022) research summary and analysis constitutes a scientific assessment of threats that farmed American mink (*Neovison vison*) pose to human health and animal health, particularly as related to the susceptibility of American mink to SARS-CoV-2 and their ability to pass it on to humans, other mink or wildlife. This report addresses other closely related questions and concerns. *Supplement 1* provides a fuller expanded exposition of seven key public health risks from farmed mink than in this summary review. *Supplement 2* supplies background information on wild and farmed mink and their relationship to COVID-19 risk. *Supplement 3* offers evidence that farmed mink are an invasive and injurious species. *Supplement 4* provides details of studies of mutant variant SARS-CoV-2 from mink. *Supplement 5* presents annotated references and a comprehensive bibliography.

### ***II - Underlying risk factors posed by captive mink on farms***

There are *seven major reasons* why farmed mink place public health at risk from SARS-CoV-2:

1. Farmed mink are the only animals besides people that transmit, sicken and die in large numbers of COVID-19.
2. Mink are the only animals that if infected can spill the COVID-19 virus back to people often in mutated form.
3. Mink are the only animals with a large potential wild animal reservoir for COVID-19 i.e. the millions of wild or feral mink across the entire Northern hemisphere that could become permanently infected.
4. Mink are a top candidate as the “missing zoonotic link” between bats and people (according to the World Health Organization) that spawned or accelerated the COVID-19 pandemic.
5. Mink are a proven source of novel virus variants (mutants) that may compromise human vaccines or treatment effectiveness or possess increased human virulence or transmissibility traits.
6. Farmed mink are raised in stressful unnatural conditions to which they cannot biologically adapt which maximizes chances for SARS-CoV-2 infections and mutations and other zoonoses.
7. An experimental mink veterinary vaccine made by Zoetis against SARS-CoV-2 was used to vaccinate more than 90% of U.S. farmed mink in the summer and fall of 2021. The U.S. is the first nation to adopt widespread farmed mink vaccination. (China may be vaccinating its farmed mink. Finland, Russia, and some Canadian provinces are considering mink SARS-CoV-2 experimental vaccination.) Vaccines are not a panacea, however, and the strategy is costly and unproven and breakthrough infections (i.e. COVID cases occurring in fully vaccinated mink) are to be expected. In some ways, vaccines will be detrimental to COVID-19 control in mink especially in giving a false sense of biosecurity and bio-safety and if relied upon as the sole or primary means of infection control, as on most U.S. mink farms.

### III - Key findings

There are *major public health risks* from farmed mink that warrant concern and expedited action from community health and preventive medicine authorities and political leaders.

- The scientific literature, public health reports, and expert advice indicate that the farmed mink industry is a current and future *high-consequence threat* to the U.S. and global public health from COVID-19.
- Before the COVID-19 pandemic in late 2019, 36 countries had mink farming industries producing about 60 million mink pelts per year. Hundreds of thousands of mink on at least 335 mink farms in 13 countries became infected with SARS-CoV-2 in 2020 and/or 2021 (*Table 1A*).
- Farmed mink are raised in exploitative, intensive, high density, high volume, low welfare, and low hygiene conditions. Intensive farming practices, in conjunction with marginal nutrition and poor sanitation, enhance contagion among crowded, genetically homogenous mink. SARS-CoV-2 mink farm outbreaks are facilitated by housing conditions which typically consist of adjoining bare wire cages that allow for both free airflow and animal contact within their densely populated facilities.
- There are *unintended if predictable disease consequences* to raising normally solitary, isolated, and unsocial wild mink under these stressful environmental circumstances to which they are evolutionary maladapted. The same intensive confinement conditions that simplify mass-rearing of mink create ideal conditions for SARS-CoV-2 to prosper and evolve.
- Europe produced about 50% (~30 million pelts) of the global supply of mink pelts in 2019 on about 3,000 farms before the SARS-CoV-2 pandemic. The U.S. mink industry is much smaller with fewer than 100 active farms producing about 2 million mink pelts per year. In both Europe and North America, the mink industry is under severe financial duress and in long-term decline. It primarily serves an export fashion market in just a handful of countries, and not a European or North American market (*Table 1B*).
- Farmed mink are readily infected by SARS-CoV-2 and are a proven source of mutated COVID-19 virus variants that may compromise human vaccines, lessen herd immunity, decrease treatment effectiveness, and increase virus spread and human disease. *This risk is not hypothetical*: mink-origin viruses with mutated spike proteins (the human vaccine target) were detected in Michigan, Wisconsin, and several European nations in 2020.
- Mink ranches are potential COVID-19 “*super-spreader*” sites from the combination of innate mink susceptibility to infections and the unnatural, crowded, stressful, and low welfare conditions that facilitate SARS-CoV-2 infections, virus mutations, and people-to-mink, mink-to-mink and mink-to-human spread.
- Mink farming may lead to SARS-CoV-2 establishment in a wild animal zoonotic reservoir, including wild or feral mink or other common wildlife species (e.g., North American white-tailed deer or deer mice). If this occurs, the virus has the potential to *circulate indefinitely in wild animal populations*, mutate and spill back into humans when circumstances permit. U.S. zoonotic wildlife reservoirs of *rabies*, *plague*, *brucellosis*, and *tuberculosis* routinely spillover into domestic animals (pets, livestock) and people, so the potential for mink to introduce this disease into free-roaming

populations is not hypothetical. Bovine tuberculosis in European badgers and rabies in foxes are European examples of wildlife zoonotic reservoirs.

- Farmed mink *routinely escape captivity* and may establish long-term self-sustaining feral populations (as in Europe) or hybridize with wild mink (as in North America). At double the adult size of wild mink, farmed mink can physically dominate and may compete with native North American wild mink in a manner analogous to an invasive species.
- As carriers of SARS-CoV-2 and other animal or zoonotic pathogens, escaped or released *farmed mink are serious disease vectors, ecological disruptors, and injurious species to native U.S. and European wildlife*. SARS-CoV-2 spillover from farmed mink to native wildlife may decrease biodiversity and damage natural ecosystems. Mustelids such as wild mink and the endangered North American black-footed ferret are particularly vulnerable to disease and eco-mischief from farmed mink in the US. Feral American mink threaten the endangered European mink via competitive ecological displacement throughout its native European habitat.
- It is estimated that *at least 20 million mink* died or were euthanized due to exposure to or infection with SARS-CoV-2, mostly from mandatory culls in Denmark (17M) and the Netherlands (2M). We estimate 7.9 million mink in Europe and North America were present on 435 farms with known outbreaks (**Table 1A**). Assuming a 90% mink infection rate on these 435 farms, about 7.2 *million farmed mink were infected globally* with SARS-CoV-2, of which *about 10% (720,000 mink) died* from COVID-19. Thus the past and future appearance of dangerous farmed mink-origin SARS-CoV-2 “escape mutants” should not surprise.
- In 18 confirmed U.S. farmed mink SARS-CoV-2 outbreaks in four states, 21,528 out of 205,657 exposed mink died of COVID-19, a 10.5% mortality rate (**Table 2**). This is *6.2-fold higher mink mortality* vs. U.S. human pre-vaccine COVID-19 mortality of 1.7%. Assuming a 90% infection rate, 185,000 U.S. mink were infected. Like people, some mink harbor asymptomatic infections so these numbers are almost certainly under-estimates.
- Mink ranching represents a *substantial and unpredictable zoonotic hazard*: (1) Farmed mink may be the missing link in the bat-to-human transmission chain that fast-tracked the COVID-19 pandemic; (2) Farmed mink mutants may compromise human vaccines or therapies and increase human morbidity and mortality; (3) Farmed mink may lead to the permanent entrenchment of the virus in native wildlife. The question is, “*Is U.S. mink farming worth the risk?*”
- Digby and colleagues (2021) recently demonstrated that the worldwide factory farming of wild carnivores - such as mink, raccoon dogs, foxes, and civet cats for fur or food - is extremely risky to public health. This is because Carnivore mammals have built-in immune system deficiencies that permit them to become infected and then carry (rather than kill) zoonotic viruses, bacteria, and parasites. These parasites and pathogens can then be transmitted to other susceptible animals and people. Keeping large numbers of farmed carnivores crowded together on industrial “farms” creates perfect conditions for the pathogens to be carried, to amplify their numbers, and, perhaps most importantly, to mutate into more dangerous variants.

#### ***IV - Key policy conclusions and recommendations***

Western governments *rightly criticized China in 2003* after the first SARS-1 epidemic for not dismantling its vast network of live wildlife “wet” markets. But throughout Europe and North America, we have a *comparable public health threat from farmed wild mink*, a risk that will worsen if the SARS-CoV-2 virus expands into wild or feral mink.

A more comprehensive and coordinated global response is needed to tackle SARS-CoV-2 infections in mustelids and mitigate the risk of future animal and human coronavirus outbreaks (Díaz et al 2021). Most importantly, parliaments should initiate and pass legislation to *ban mink farming* as it poses a serious threat to human health. Absent a *nationwide, perhaps even global strategy to ban farmed mink*, we risk *worsening or prolonging* the COVID-19 pandemic via the spawning and spread of farmed mink variants against which vaccines may be less effective, along with fostering ideal conditions for wildlife-human disease transmission that could propel a new COVID-19 pandemic.

- The U.S. Fish and Wildlife Service should declare captive American mink an “*injurious species*” under authority granted to it by the U.S. Congress under the Lacey Act.
- Mink-farming nations should *phase out and buy out* all mink farms, actively surveilling and quarantining them until that process is complete. Mink farmers should be fairly compensated just as other industries that were severely damaged by the pandemic have been reimbursed. Europe has generally taken a proactive and precautionary approach using active surveillance and culling of infected mink farms. In contrast, the U.S. and Canadian public health response to SARS-CoV-2 in farmed mink has been passive and tepid at best to date, relying almost solely on vaccination.
- These recommended actions are grounded on the following social and epidemiological concerns:
  - *Animal care and humane treatment*: American mink are solitary, even anti-social, semi-aquatic animals. They fare very poorly in cage confinement in overcrowded settings.
  - *Cost-effectiveness*: In most of Europe and North America, mink farming is a small industry with no domestic market for a luxury good. The mink industry has the potential to cost nations billions of dollars and to take human life on an enormous scale should a mink farm incubate a novel variant that spreads into wild animal populations and/or into the human population. In essence, mink farms are reservoirs-in-waiting for future spillback of SARS-CoV-2 from animals to humans or from caged animals to wild animals.
  - *Precautionary public health principles*: The world is still in the grip of a pandemic, and the U.S. and other nations have made other sacrifices - from mask-wearing to business shutdowns to social distancing and social isolation requirements. By quickly winding down a declining mink farming industry, with a compensation program to benefit the farmers, the government is taking actions in line with other urgent responses to the biggest pandemic that has hit the world in a century.
  - *Proportionate public health response*: Given the modest (EU) to small size (US) of the mink industry versus the enormous potential adverse consequences of continuing mink ranching, and the unique susceptibility of mink to the virus, it would be derelict of Europe, the U.S. and Canada not to take action. The minuscule and dying farmed mink industry potentially puts our multi-billion-dollar vaccination campaign and our national herd immunity strategies at risk.

- Recent legislative and executive actions in the European Union (EU) and the United States
  - On June 28, 2021, at the EU’s Agriculture and Fisheries Council, Ministers from the Netherlands and Austria advanced a discussion paper calling upon the European Commission “to undertake action leading to the end of fur farming in Europe.” The request considers animal welfare and ethical considerations in fur farming but also public health and animal health risks due to the animals (mink) SARS-CoV-2 susceptibility. The paper received support from 10 Member States: Belgium, Germany, Luxemburg, Slovakia, Italy, France, Ireland, Poland, Slovenia, and Bulgaria in addition to the Netherlands and Austria (EFA 2021). Support appears to be expanding.
  - On July 1, 2021, bipartisan federal legislation (H.R. 4310), the “Minks in Narrowly Kept Spaces Are Superspreaders Act (MINKS Act)”, was introduced into the U.S. House of Representatives to ban mink farming motivated by concerns about mink farms in spreading SARS-CoV-2 and risking public health, native wildlife populations, and U.S. natural ecosystems (AWA 2021).
  - Acknowledging animal cruelty, bioethics concerns, and zoonotic threats to public health from COVID-19, fur-producing nations e.g. the Netherlands, Poland, Ireland, Estonia, and France, and the Canadian province of British Columbia, announced the permanent closures of mink and other fur farms. Denmark, Sweden, and Italy temporarily banned mink farming due to SARS-CoV-2 concerns, with permanent bans on the horizon. Nations with long-standing fur farming prohibitions e.g. the United Kingdom are moving towards restrictions on fur sales. Austria, Belgium, Croatia, Slovenia, Bosnia and Herzegovina, Serbia, Macedonia, and Norway previously banned fur farming. Thus 15 European nations ban or soon will ban fur farming.
  - Coordinated and rapid executive, legislative, and community action are needed to shut down the farmed mink industry in the near term. While there is a strong anti-fur legislative and public sentiment in Europe, the attitude in North America appears less robust. With Denmark and the Netherlands leaving the market, there is potential for a worldwide shortage of mink pelts. Mink farmers in the U.S, Canada, China, and elsewhere could quickly expand mink production to fill this new demand for fur, simultaneously increasing both mink suffering and public health SARS-CoV-2 risk. The Chinese are the biggest buyers of furs representing 80% of the fur trade. Surveys of high-income Chinese show high demand for fur (Mancl 2021).
- Control of SARS-CoV-2 mink farm outbreaks differs greatly between countries, ranging from a total ban on mink farming in the Netherlands, a temporary industry shutdown in Denmark, to quarantine, disinfection, and increased biosecurity in the United States (Diaz et al 2021).
  - In Europe, most mink-rearing countries instituted an active surveillance system for the rapid detection of subclinical and clinical cases in farmed mink by summer 2020. This consists of mandatory notification, an early warning system linked to mink mortalities, and serological screening of farms for anti-SARS-CoV-2 antibodies. Control measures included culling of all animals on infected farms, testing of symptomatic farm staff, intensified biosecurity, personal protective equipment (PPE) for staff exposed to animals, and a 10-day waiting period for employees working in different locations (Diaz et al 2021). Extensive viral sequencing identified infected employee-to-mink as an introduction route for some farms. In the Netherlands, the nationwide culls implemented in late 2020 and the moving forward of an industry ban by three years decisively eliminated the risk of hosting a farmed mink reservoir for SARS-CoV-2.

- The outbreak response in the United States has been largely passive (e.g. mink farmer self-reporting) and limited to increased biosecurity, quarantine, and disinfection of affected units. Culling has not been implemented; testing is restricted to symptomatic animals. PPE and testing of farm workers are encouraged but not mandated. Case identification relies on passive surveillance i.e. not actively looking for infected farms. Unlike in Europe, mink vaccination is the prime intervention in the U.S..
- The degree to which passive mink farm surveillance underestimates SARS-CoV-2 outbreaks was recently demonstrated: when Sweden actively surveyed 26 of their 28 active operating mink farms in 2021, they found 23 farms (88.4%) were SARS-CoV-2 sero-positive i.e. previously but unknown to be infected (Stahl 2021).
- Regulatory frameworks and cohesive national and global responses are needed including active surveillance for both spillover events and variants (from virus sequencing) linked to mink farms, as well as effective control measures (e.g. culling) to combat unabated spread (Diaz et al 2021). Imprecise available estimates of the number, size, conditions, and especially the location of fur farms highlight the need for regulatory oversight (Koopmans 2021).

## **V - Methodology**

We carefully reviewed more than 100 peer-reviewed scientific publications on mink and SARS-CoV-2 from molecular virology to on-farm epidemiology to mink-origin human COVID-19 outbreaks (<https://pubmed.ncbi.nlm.nih.gov/?term=mink+sars-cov-2+covid-19>). We also carefully examined numerous public health, science media, animal welfare, and mink industry reports. We recommend several cited studies for readers, but two in particular: (1) Fenollar F, Mediannikov O, Maurin M et al, 2021. Mink, SARS-CoV-2, and the human-animal interface. *Front Microbiol.* 2021 Apr 1;12:663815. <https://pubmed.ncbi.nlm.nih.gov/33868218/> & (2) Díaz AV, Walker M, Webster JP, 2021. Surveillance and control of SARS-CoV-2 in mustelids: An evolutionary perspective. *Evol Appl.* 2021 Nov 6:10.1111/eva.13310. <https://onlinelibrary.wiley.com/doi/10.1111/eva.13310>.

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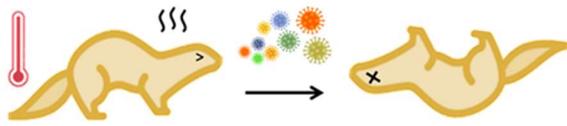
Keen earned his veterinary medicine and epidemiology doctorate degrees from the University of Illinois at Urbana-Champaign. He was a senior veterinary researcher focused on livestock and zoonotic infections with the USDA Agricultural Research Service in Nebraska for 15 years and later faculty at the University of Nebraska-Lincoln School of Veterinary Medicine for 13 years. His specific expertise is emerging and zoonotic infectious diseases of farmed animals. He has broad field experience in outbreak investigation and animal disease control including enteric zoonotic bacteria from livestock in the U.S., Foot and Mouth Disease in the United Kingdom, and African Swine Fever in the Caucasus. Keen lives on his family's 140-year old grain farm in South Dakota. He is Director of Veterinary Sciences at the Center for a Humane Economy.

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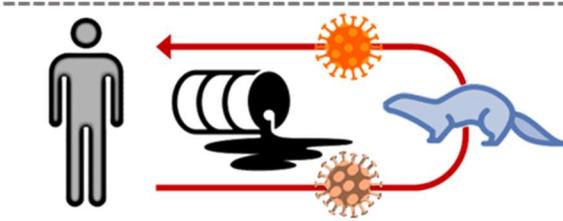
## Pictogram overview of Supplement 1

### Supplement 1: Seven public health risks from farmed mink

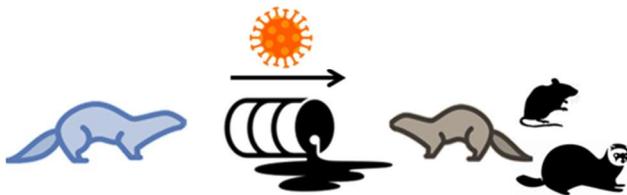


1 - Most mink on farms get infected; many sicken & die

**Supplement 5:**  
Cited & annotated references for entire report



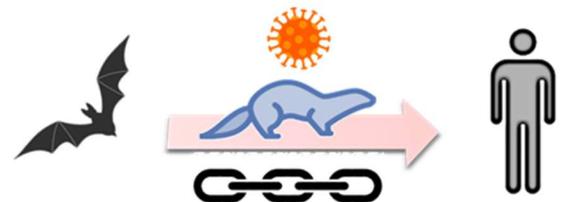
2 - Two-way transmission: spill-over & spill-back



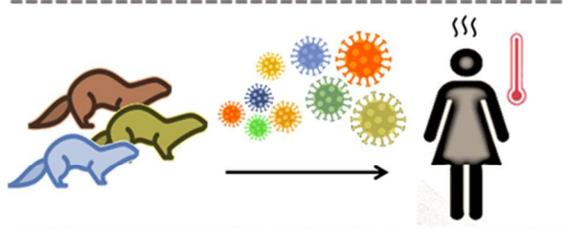
3 - Spill-over to wildlife will create an ineradicable virus reservoir



**Supplement 3:**  
Escaped & feral farmed mink are invasive & injure eco-systems



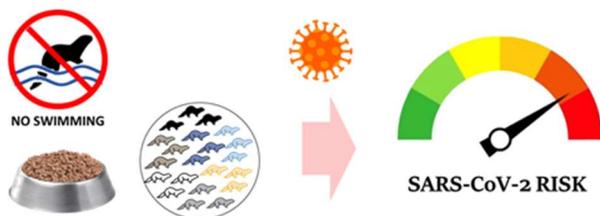
4 - Are mink the missing link in the bat-to-human virus evolution chain?



5 - Mink virus factories create mutants that compromise human vaccines & therapy



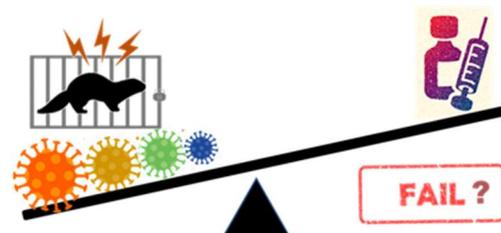
**Supplement 4:**  
Harmful traits of virus mutant variants from farmed mink



6 - Distressful mink farm life amplifies virus spread & mutants



**Supplement 2:**  
Totally unnatural & high stress life of farmed mink



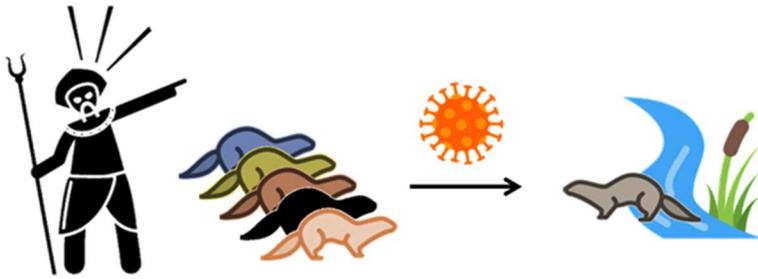
7 - Mink vaccines may fail due to mink distress, mutants & high viral loads

## Pictogram overview of Supplements 2 to 5

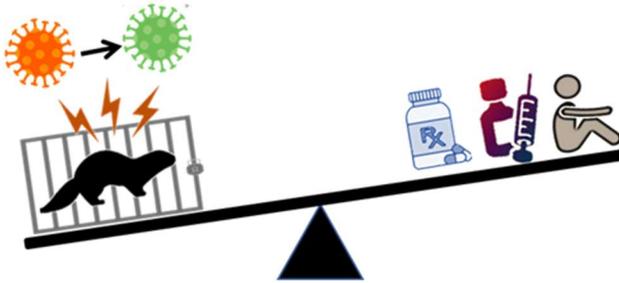
**Supplement 2:** Totally unnatural & stressful life of farmed mink



**Supplement 3:** Escaped & feral farmed mink are invasive & injurious to human health, wild mink & natural eco-systems



**Supplement 4:** Harmful virus mutant variants from farmed mink may reduce human vaccine & drug therapy efficacy



**Supplement 5:** Cited references are primarily peer-reviewed scientific journals augmented by secondary sources



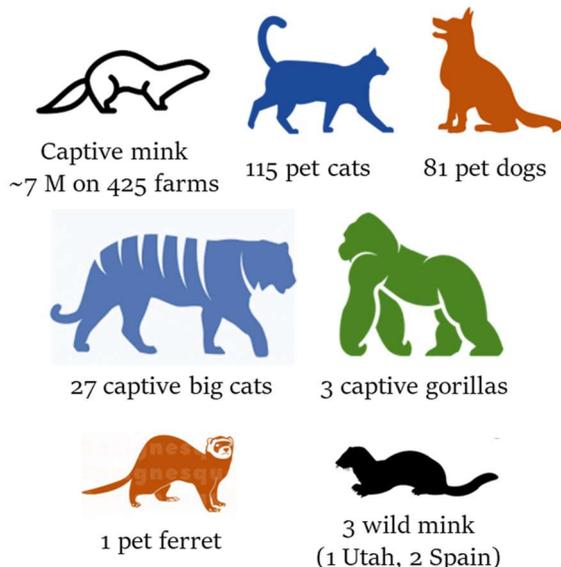
## Supplement 1 - Documentation of seven reasons why farmed mink place public health at risk from SARS-CoV-2

### 1. Reason #1 - Mink are hyper-susceptible to SARS-2 infection, disease & death

Pre-CoVID-19 pandemic, there were about 60 million farmed mink reared worldwide. About 20 million of the 30 million farmed mink in Europe either died from COVID-19 or were euthanized to reduce public health risk (e.g. Oreshkova et al 2020; Enserink 2020; Hansen 2021). Denmark, the world's largest mink producer, euthanized its 17 million farmed mink, including breeding stock, and provided \$3.1 billion in compensation to farmers (Larsen et al 2021; Reuters 2021). An estimated third of the global farmed mink total were culled or died from SARS-CoV-2 in 2020.

There were at least 435 farmed mink SARS-CoV-2 outbreaks in Europe and North American in 13 nations that killed thousands of mink. The most recent outbreaks occurred in April 2021 in Latvia, in May 2021 in British Columbia, Canada, and in Spain (six) and Poland (2) in June 2021 (CVI-Poland 2021). All major mink pelt-producing countries *except China* had mink farm outbreaks. Twenty-three percent of 1,856 mink farms in these 13 countries had verified SARS-CoV-2 outbreaks. See **Table 1A**, **Table 1B**, and **Figure 1**.

- There were 18 known outbreaks on U.S. mink farms that killed >21,500 mink (Fenollar et al 2021). See **Table 2**. With a possible estimate of just 60 to 80 active U.S. mink farms, this constitutes 20 to 30 percent of all U.S. farms as infected.
- Most (>80%) mink who contract an infection sicken over two weeks after a virus emerges on a farm. However, mink outbreaks may be underestimated as the infection can be clinically silent, as demonstrated in Denmark where up to a third of farms were sub-clinically infected.
- *Hammer et al 2021*: “A high proportion of mink on farms can be infected with SARS-CoV-2 within a few days, which may provide major virus exposure to persons working with mink. The infections ... occurred with little clinical disease or increase in death making it difficult to detect the spread of infection; thus, mink farms could represent a serious, unrecognized animal reservoir for SARS-CoV-2.”



#### Box 1 - Natural SARS-CoV-2 infections in animals as of February 2021 (AVMA 2021)

Many countries report natural SARS-CoV-2 infections in non-human animals. All initial animal infections are believed to have been acquired from contact with infected people.

Farmed mink are the only animals in which infection is sustained and not a transmission dead-end. Given a farm-level 90% infection rate and 10% mortality rates in 435 outbreaks, about 7.2 million farmed mink were infected globally with SARS-CoV-2 and about 712,000 mink died of COVID-19. Infected wild and feral mink were trapped in Utah and Spain.

**Table 1A- Global mink farm SARS-CoV-2 outbreaks (n=435) - April 2020 to October 2021. Blue font = countries with mink farm outbreaks in 2021**

Country	Infected farms		No. farmed mink & farms 2020 (pre-COVID-19)	1st reported outbreak	Farm & national SARS-CoV-2 response
	No.	%			
Netherlands	69	55%	4.5 million; 125 farms	April 2020	Signs: respiratory disease & increased mortality; quarantine then cull affected farms starting June 2020; ban mink farming Jan 2021; >2M mink euthanized
Denmark	290	25%	17 million; 15 million culled; 1140 farms	June 2020	1/3 infected farms w/ no clinical signs (Boklund et al 2021); cull all mink in country in Nov 2020. >100 infected mink escaped farms; payment 30 kroner (\$4.91) per mink to all farmers affected by culls; Ban mink farming. \$3.1 billion in farmer compensation
Spain	9	24%	750K; 38 farms	July 2020	Euthanize all mink on infected farms
United States	18	15% to 23%	2.0 million; 80 to 120 farms in up to 23 states; exact numbers unknown	Aug 2020	UT Aug 17, 2020; WI & MI on Oct 8 & 9, 2020; OR on Nov 27, 2020; mortality rates of infected mink varied by farms from 0% to 42% Farms: UT, MI, WI, OR; Feral mink: UT, OR; USDA ordered quarantines & testing but no mandated mass culling
Sweden	14	40%	600K; 35 farms 2020; 28 in 2021	Oct 2020	Quarantine farms; no mandatory cull; 23 of 26 sero-surveyed farms POSITIVE
Italy	2	33%	60K; 6 farms	Oct 2020	Culled 26K mink (43% of Italy's mink) on two infected farms
Greece	22	24%	1.2 million; 90 farms	Nov 2020	Quarantine farms; no mandatory cull
France	1	25%	20K; 4 farms	Nov 2020	Euthanize all mink on infected farms
Lithuania	2	2%	1.6 M; 86 farms	Nov 2020	Quarantine farms; no mandatory cull
Canada	3	5%	1.0 million; 60 farms	Dec 2020	200 dead on 15K farm #1; 23 dead on 1K farm #2; 13 POS on 25K farm; quarantine only; new farm moratorium
Poland	3	<1%	5.1 million; 130 farms	Dec 2020	Outbreak detected by active surveillance; Poland is largest post-COVID mink producer in Europe
Belarus	1	13%	650K, 8 farms	Feb 2021	No outbreak details available.
Latvia	1	11%	130K; 9 farms	April 2021	Infected farm has 60K mink
China	?	?	21M (2018); 12M (2019); 3K farms	NA	No reports of mink outbreaks or infections

**Table 1B - Major nation and worldwide farmed mink pelt production (millions), 2017 to 2021 in 36 mink-rearing nations**

Major mink rearing countries	Mink farm outbreaks?	Vaccines?	Mink pelts produced				
			2017	2018	2019	2020	2021
China	None reported	Yes?	19	17	11	4	4
Denmark	Yes: 290 of 1140 farms	No	17.9	17.1	12.8	5.6	0
Poland	Yes: 3 of 130 farms	No	8	6	5	4.5	5
Netherlands	Yes: 69 of 125 farms	No	5.1	5	4.5	1	0
United States	Yes: 18 of ~80 farms	Yes	3.4	3.1	2.7	1.8	1.25
Canada	Yes: 3 of 60 farms	Yes - planned	3.0	2.5	2.0	0.9	0.9
Russia	None reported	Yes - planned	1.9	1.7	1.6	1.3	1.3
Finland	None reported	Yes - planned	1.1	0.8	0.7	0.78	0.85
Greece	Yes: 22 of 90 farms	No	1.7	1.6	1.5	1.2	1.5
Lithuania	Yes: 2 of 86 farms	No	1.4	1.3	1.1	1.5	1.7
<i>Subtotals</i>	<i>Seven of 10 major nations</i>	<i>Four of 10 major nations</i>	62.5	56.1	42.9	22.6	16.5
Rest of world	Six additional nations		5.5	5.9	13.1	4.4	3.5
<b>World totals</b>	<b>13 nations, 434 farms</b>		<b>68</b>	<b>62</b>	<b>56</b>	<b>27</b>	<b>20</b>

Annual change in production:  -10% -10% -52% -26%

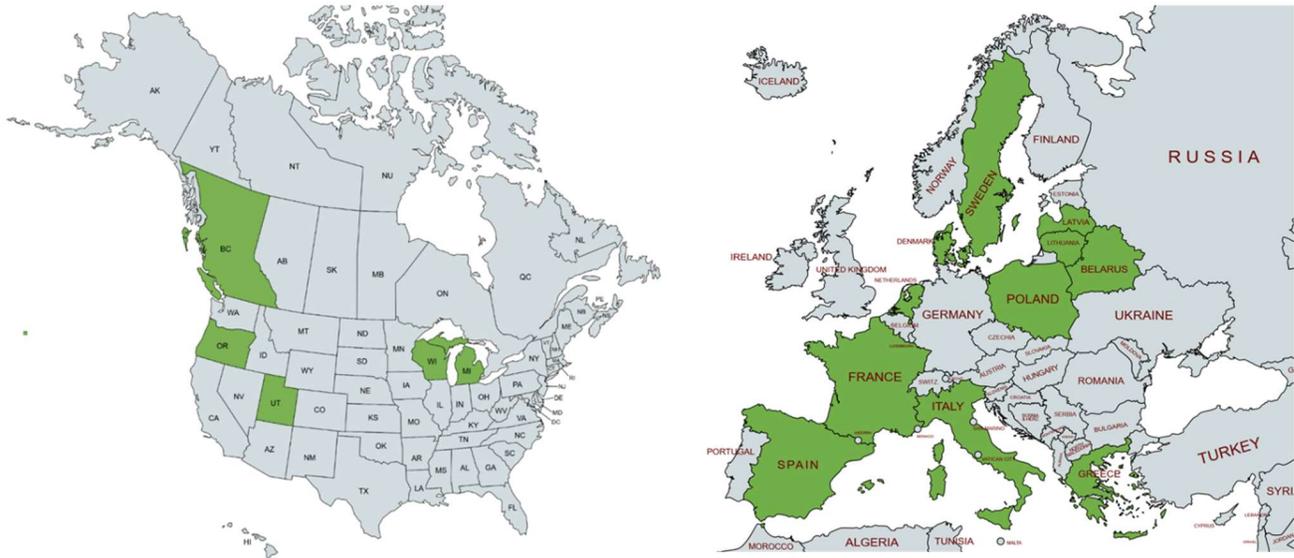
Modified from: <https://www.wearefur.com/wp-content/uploads/2021/06/Global-fur-retail-value-May-2021-Henning-study.pdf>

**Table 2 - Mortality rates in mink infected by SARS-CoV-2 on 18 U.S. mink farms in four states**

Sort	Date of outbreak	State	No. dead mink / No. mink on farm (% died)	Sources (Accessed Feb 03, 2021)
1	7/26/2020	UT	3,524/20,000 (16.3%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35412">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35412</a> ; <a href="https://promedmail.org/promed-post/?id=7692815">https://promedmail.org/promed-post/?id=7692815</a>
2	8/2/2020	UT	1,451/8,983 (16.2%)	As previous
3	8/3/2020	UT	1,554/6,326 (24.6%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=35525">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=35525</a>
4	8/5/2020	UT	1,119/3,643 (30.7%)	As previous
5	8/15/2020	UT	205/1,705 (12%)	As previous
6	9/7/2020	UT	146/600 (24.3%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35946">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35946</a>
7	9/20/2020	UT	247/14,000 (1.8%)	As previous
8	9/24/2020	UT	59/1,500 (3.9%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35857">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35857</a>
9	9/27/2020	MI	2,000/17,000 (11.8%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35973">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35973</a>
10	9/29/2020	UT	126/300 (42%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36151">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36151</a>
11	9/30/2020	WI	1,800/14,600 (12.3%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35973">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=35973</a>
12	10/8/2020	UT	373/3,000 (12.4%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36580">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36580</a>
13	10/19/2020	WI	2,200/22,500 (9.8%)	As previous
14	10/22/2020	UT	585/13,200 (4.4%)	As previous
15	10/22/2020	OR	No excess mortality / 12,000	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=36731">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=36731</a>
16	10/25/2020	UT	739/38,000 (2%)	<a href="https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36580">https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&amp;reportid=36580</a>
17	11/4/2020	WI	3,400/22,600 (15%)	<a href="https://promedmail.org/promed-post/?id=7923387">https://promedmail.org/promed-post/?id=7923387</a> ; Simmons 2021
18	11/5/2020	WI	2000/5700 (35%)	As previous

A total of 21,528 out of 205,657 mink in the U.S. died of COVID-19 = 10.5% mortality rate. Note: This is 6.2-fold higher than the human pre-vaccine COVID-19 mortality rate of 1.7% in the U.S. Assuming a farm-level infection rate of 90%, about 185,000 mink were infected. Farm-level mortality ranged from 0% to 42% with a median of 12.4%. The median infected mink ranch size was 10,492 animals. Sharun and colleagues (2020) provide a good review of SARS-CoV-2 infection and disease in mink. (Note - Table 2 above was modified from Fenollar et al 2021).

**Figure 1 - Thirteen countries, four U.S. states, and one Canadian province with farmed mink SARS-CoV-2 outbreaks, 2020-2021**



## ***2. Reason #2 - Mink catch SARS-CoV-2 from people (spill-over) and return the favor (spill-back)***

Mink-to-human spread is documented in Denmark (Hammer et al 2020), the Netherlands, (Oude Munnink et al 2021), Poland (Domańska-Blicharz et al 2021), and the United States in Michigan (Kravitz & Fortis 2021; CDC 2021; Cai & Cai 2021). Mink-to-human transmission is likely to have occurred in France (Fournier et al 2021). Thus mink ranchers were/are a high priority group for the COVID-19 vaccine as an occupational at-risk group (Simmons 2021).

- *CDC 2021*: “Investigations found that mink from a Michigan farm and a small number of people were infected with SARS-CoV-2 that contained unique mink-related mutations (changes in the virus’s genetic material). This suggests mink to human spread might have occurred.”
- The *European Centre for Disease Prevention and Control (ECDC 2021)* stated that between June 2020 and January 2021, Denmark reported over 1,000 human cases of infection with a mink-related variant of the virus with Danish estimates as high as 4,000 human cases caused by mink variants.
- In the Netherlands, mink farm workers infected 68 percent of their family members, friends, and others with whom they interacted. *Farm workers acted as virus super spreaders*. When Denmark and the Netherlands experienced these alarming cases of bilateral transmission, public health authorities took decisive action and opted to cull all mink, collectively more than 20 million animals. After that culling occurred, no additional human cases linked to mink variants were reported in these two nations (Oude Munnink et al 2021).
- In the Netherlands between May and September 2020, up to 40% of human cases were mink-derived (Konishi 2021).

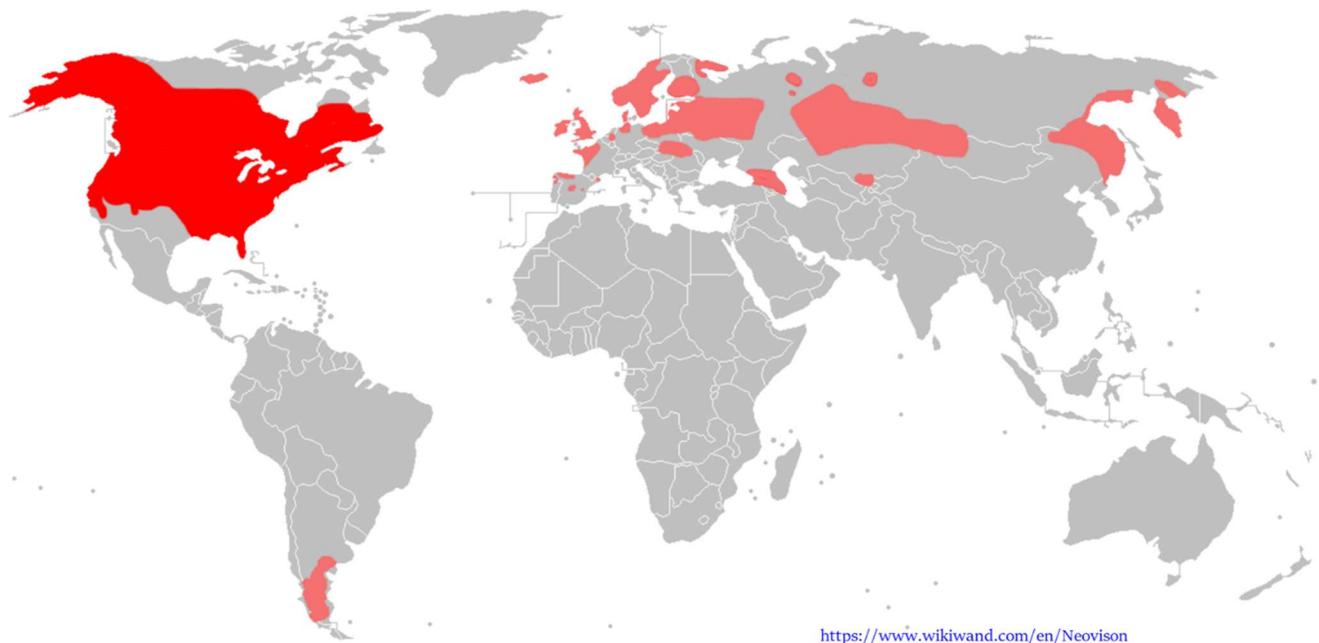
- An epidemiologic investigation of the simultaneous SARS-CoV-2 outbreaks on mink farms and in adjacent human communities in weeks 24–51 of 2020 in Denmark showed: (1) SARS-CoV-2 outbreaks on mink farms in a municipality associated with an increase in weekly human incidence rates by about 75%; with spatial spillover effects to neighboring municipalities also observed and (2) For control of human outbreaks, culling of mink in combination with a local lockdown were the most effective approach to infection control (Schmidt & Mitze 2021).

### **3. Reason #3 - Escaped, feral & wild mink are an infection reservoir for human SARS-CoV-2.**

There is a risk that the *SARS-CoV-2 virus will become established and spread among the millions of wild or feral mink populations in the U.S. or other wild animal species*. This will greatly complicate control efforts by becoming a perpetual human outbreak source. Endangered U.S. wild mustelids e.g. wolverines, black-footed ferrets, fishers may also be at risk from mink-borne SARS-CoV-2.

- North American mink, either wild or escaped feral animals, inhabit most of North America, large swaths of Eurasia, and the cone of South America (**Figure 2**). American mink were first imported into Europe by fur farmers for their superior pelts in the 1920s. They were deliberately introduced into the wild in the former Soviet Union and escaped fur farms in Europe. These are regions where SARS-CoV-2 could become endemic in wild or feral mink as a perpetual source of sporadic human COVID-19 outbreaks.

**Figure 2 - Current native (red, North America) and introduced (pink, Eurasia, South America) distributions of free-ranging American mink (*Neovison vison*).**



- Some escaped American mink thrive in the European wild. Escapees established self-sustaining populations in England, France, Germany, Iceland, Ireland, Norway, Poland, Scotland, and Sweden (Lanese 2020). Feral farmed American mink are up to twice the size of wild American mink,

especially males, so that escaped farm mink often dominate wild mink even in their native North America (Fenollar 2021).

- Outside their natural range, American mink are invasive, and often have negative impacts on native taxa (including prey species and other predators that they outcompete and sometimes kill. Across northern Europe and Asia, non-native wild or feral North American mink (*Neovison vison*) largely fill the vacant niche of the critically endangered Eurasian mink (*Mustela lutreola*). Eurasian mink were over-hunted and are out-competed, displaced, or killed by the larger, more aggressive American mink.
- Wild mink population density and frequency of contact in the wild are much lower than in captive mink. SARS-Cov-2 outbreaks in farmed mink revealed rapid virus evolution and spill-over transmission to humans. Rapid mutation of the virus and the potential emergence of host-adapted variants may be less likely in wild populations but cannot be ruled out especially over time. Even in short periods, amino acid polymorphisms were identified in closely related experimentally infected ferrets that might influence spike protein function. The spike protein is the target of all COVID-19 vaccines (Delahey et al 2021)

#### **A - Peer-reviewed studies & public health reports underscore SARS-2 wildlife reservoir threat**

*Manes et al 2020*: “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 and with bovine tuberculosis in badgers. 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.”

*ProMed-mail Fri 11 Dec 2020*: “The USDA National Veterinary Services Lab (NVSL) confirmed SARS-CoV-2 by real-time RT-PCR and sequencing of a nasal swab collected from a free-ranging, wild mink sampled in Utah near an infected mink farm. This is the first free-ranging, native wild animal confirmed with SARS-CoV-2. The sequence of the viral genome from the wild mink sample at NVSL was indistinguishable from those obtained from the farmed mink.”

*Aguiló-Gisbert et al 2021*: “We have detected SARS-CoV-2 RNA in two wild American minks (*Neovison vison*) in Valencian Community (Eastern Spain) during invasive species trapping campaigns. The animals were trapped from areas known for harbouring self-sustained populations, far away from the nearest fur farm. SARS-CoV-2 RNA was detected in mesenteric lymph nodes samples by RT-PCR. A partial region of the Spike protein gene was amplified and sequence obtaining a 397 nt [nucleotide] size sequence. Phylogenetic analysis showed that both sequences were identical to the consensus variant SARS CoV-2 sequence [from Wuhan]. This research describes the first infection report of a true wild American mink not related to infected fur farms or direct contact with humans, which is believed to be the first example of wild animals in which SARS-CoV-2 has been detected.”

*Hoffman et al 2021*: “The transmission of SARS-CoV-2 to wild minks is an alarming observation as such transmission events might generate a permanent natural reservoir for such viruses and new emerging variants that could represent a future threat to wildlife and human health”.

*Koopmans 2021*: “Although the number of human cases from contact with infected mink is negligible compared with those from the human epidemic, the risk of reservoir establishment with unforeseeable consequences has been the basis for the decisions to cull farms in the Netherlands and Denmark.”

*Mallapaty 2021*: “In the current stage of the pandemic, with hundreds of thousands of confirmed COVID-19 infections every day, people are still driving transmission of SARS-CoV-2. But years from now, when community spread has been suppressed, a reservoir of SARS-CoV-2 in free-roaming animals could become a recalcitrant source of new flare-ups.”

*Fagre et al 2021*: “A significant concern is that SARS-CoV-2 could establish in natural wildlife populations that could lead to transmission events to humans. We have determined that deer mice are susceptible to SARS-CoV-2 and that virus can persist for up to 21 days. Moreover, efficient transmission to other deer mice occurred, suggesting the potential for sustained persistence in natural populations of deer mice.”

*Lu et al 2021*: In The Netherlands in 2021, “Throat swabs of two escaped minks tested positive for SARS-CoV-2. The two minks were caught 450 and 650 metres away from culled mink farm NB58 and NB59, respectively (8 and 9 days after culling).”

## **B - Media and other reports echo scientific concerns over SARS-CoV-2 in wildlife reservoirs**

*Ehrlich 2020*: “A mink caught outside a farm in Oregon in mid-December has tested positive for low-levels of the coronavirus. State officials believe the mink escaped from a small farm that was already under quarantine because of a coronavirus outbreak among mink and humans.”

*Kevany 2020*: “Professor Marion Koopmans, head of viroscience at Rotterdam’s Erasmus University, in an email to The Guardian said: “SARS-CoV-2 could potentially continue to circulate in large-scale farms or be introduced to escaped and wild mustelids [weasels, badgers, otters, ferrets, martens, minks and wolverines] or other wildlife” and then “in theory, as avian flu and swine influenza viruses do, continue to evolve in their animal hosts, constituting a permanent pandemic threat to humans and animals.”

*Schlanger 2020*: “I would really like to be wrong, but I fear mink are just the tip of the iceberg of what could be coming,” said Ilaria Capua, a veterinarian and virologist. “If the virus keeps spilling over into wild animals, it could circulate in parallel and keep reseeding outbreaks among humans.”

*Schlanger 2020*: “But the mink outbreak raises another fear - if the coronavirus escapes into the wild mink population, COVID-19 could become an entrenched and uncontrolled animal disease, wreaking havoc on animal communities and probably also occasionally infecting people. ‘On a ranch, you can quarantine them. When you have a wild population, that’s impossible; you can’t stop them all,’ [Keith] Poulsen said.”

*Quammen 2021*: “Five years from now, when much of the world’s population will have been vaccinated against COVID-19 but maybe a billion people won’t, either for lack of opportunity or by stubborn refusal, the virus will still be with us. It will circulate among the unvaccinated, sometimes inconspicuously, sometimes causing severe illness or death, and it could also abide among wildlife populations, mutating and evolving in ways no one can predict. If it crosses back from them to us, it

may ignite new outbreaks, start us coughing again and even bring with it some ugly genomic innovations.”

*Eurogroup for Animals 2021*: “Although the probability of transmission from mink to the general human population is low, compared to human-to-human transmission, the consequences of the establishment of reservoirs of virus are unforeseeable and may constitute a permanent pandemic threat with repeated spillover. ... If the virus were to become widespread among wild or farmed minks, it may continue to evolve in those animals. In such a scenario, the virus could accumulate mutations that might not occur in humans, potentially allowing the virus to jump to other types of animals and make them sick or transmit a new, possibly more virulent strain back to people.”

*Fine Maron 2021*: “We must avoid an animal reservoir of the disease,” [Ian Lipkin] says. The virus, circulating among a population of animals may continue to evolve and perhaps jump back and forth between humans and that species, potentially becoming more transmissible or deadly as it replicates”, W. Ian Lipkin, the director of Columbia University’s Center for Infection and Immunity.”

*Skotnes-Brown & Lynteris 2021*: “The long-term epidemiological, environmental and socio-economic consequences of SARS-CoV-2 establishing itself in wild and peri-domestic animals, including rodents, are presently unknowable but they are not unimaginable. In a recent letter to the *BMJ*, Stephen Green and Lorenzo Cladi argued that, in the context of the global COVID-19 pandemic and the numerous mutations in the virus, “scientific imaginations need to be exercised like never before to anticipate the next steps in this unfolding human tragedy,” especially as these relate to processes of reverse zoonosis. It is high time that we mobilise not only our scientific but also our historical imagination so as to anticipate and prepare for sylvatic reservoirs of SARS-CoV-2 resulting from mink farming in Europe and North America.”

The risk of SARS-CoV-2 establishment in wildlife is not hypothetical: there are several current examples in the U.S. of dangerous zoonotic diseases that are endemic in wildlife reservoirs (**Figure 3**).

### **C - Farmed and free-ranging white-tailed deer heavily infected with SARS-CoV-2**

Several recent (August 2021 and later) scientific reports found that white-tailed deer in multiple U.S. states possess either anti-SARS-CoV-2 antibodies or SARS-CoV-2 RNA signatures, sometimes at very high (>80%) prevalence. These new findings require additional research but suggest that SARS-CoV-2 may have already established a wildlife reservoir in North America. It is not known if white-tailed deer can transmit SARS-CoV-2 to people (e.g. Chandler et al 2021; Hale et al 2021; Mallapaty 2021; Palermo et al 2021)

**Figure 3 - Short & long term U.S. & global public health risks from SARS-CoV-2 in farmed mink**

**I - Short-term hazards**

- Immediate infection risk to people working on or near mink farms and their families
- Dangerous mutant SARS-CoV-2 spillback strains to broader human populations
- Sixty million farmed mink worldwide exposing thousands of people and vice-versa

**II - Long term zoonotic reservoir**

- Zoonotic SARS-CoV-2 becomes established in wild or feral mink populations
- Continuous source of new human outbreaks even after current pandemic recedes
- Many examples of wildlife as endemic reservoirs of serious zoonotic human diseases
- Eco-threat to endangered or rare wild mustelids eg black-footed ferret, wolverine, fisher



About 60% of 5,500 female bison in the Greater Yellowstone basin are infected with the zoonotic bacteria *Brucella abortus*



Tuberculosis is endemic in white-tailed deer in north-east Michigan & northern Minnesota



About 26% of 125,000 elk in Greater Yellowstone basin are infected with the zoonotic bacteria *Brucella abortus*



Plague caused by *Yersinia pestis* is endemic in prairie dogs and ground squirrels in Western states



Rabies virus variants are endemic in bats, skunks, foxes & raccoons across the entire United States



Swine brucellosis caused by the *Brucella suis* is endemic in nine million feral hogs in 35 states

*Will SARS-CoV-2 become endemic in feral, escaped and wild mink across 40 US States ?*



#### **4. Reason #4 - Are mink the “missing link” between bats and people?**

The SARS-CoV-2 ancestor virus likely came from a tropical bat in Southeast Asia that could not infect people. It is hypothesized that the bat virus then colonized an unknown vertebrate where the virus bloomed and mutated to become adept at infecting humans. Farmed mink may be the “missing link” intermediate host bridging bats and people (**Figure 4**).

For unknown reasons, bat species host thousands of different corona viruses in (apparently) peaceful evolutionary co-existence (Wong et al 2019). Scientific evidence suggests that a SARS-CoV-2 ancestor bat corona virus unable to infect people recently colonized an unknown vertebrate in which the corona virus mutated to become capable of infecting people. No one knows yet what this animal is but turtles, snakes, and pangolins have been proposed as the “missing link” intermediate host bridging bats and people (Hu et al 2021).

Recently, Chinese bat Corona virus and SARS-CoV-2 expert Shi Zhengli (Zhou & Shi 2021) and the WHO (2021) both proposed that farmed mink may be the missing zoonotic link. This hypothesis is based on:

- a - High susceptibility of mink to respiratory viruses in general and SARS-CoV-2 in particular.
- b - Large industrialized global farmed population of 60 million mink in Europe, North America, and Asia, including up to 20 million mink on 3,000 to 8,000 fur farms clustered in northeast China.
- c - Close daily farmed mink contact with many people (unlike bats, pangolins, snakes, or turtles).
- d - Widespread mink distribution in the wild as native (North America), feral, or introduced species (Eurasia) across the northern hemisphere.

*WHO 2021*: “Seeding of SARS-CoV-2 in mink populations has shown that these animals are highly susceptible as well and the current evidence available cannot rule out the possibility for minks as the primary source of SARS-CoV-2.”

*Note*: There is no direct evidence of mink (or any other wild or domestic animal) as the intermediary natural host of SARS-CoV-2 based on sampling and testing of more than 80,000 animals of various species across China in 2020 (WHO 2021). Some argue, with evidence, that the SARS-CoV-2 origin is an accidental escape of a human-adapted isolate from the Wuhan Institute of Virology or other Wuhan lab. There is no direct evidence of a lab escape either so that the post-bat SARS-CoV-2 host remains a mystery (Wade 2021).

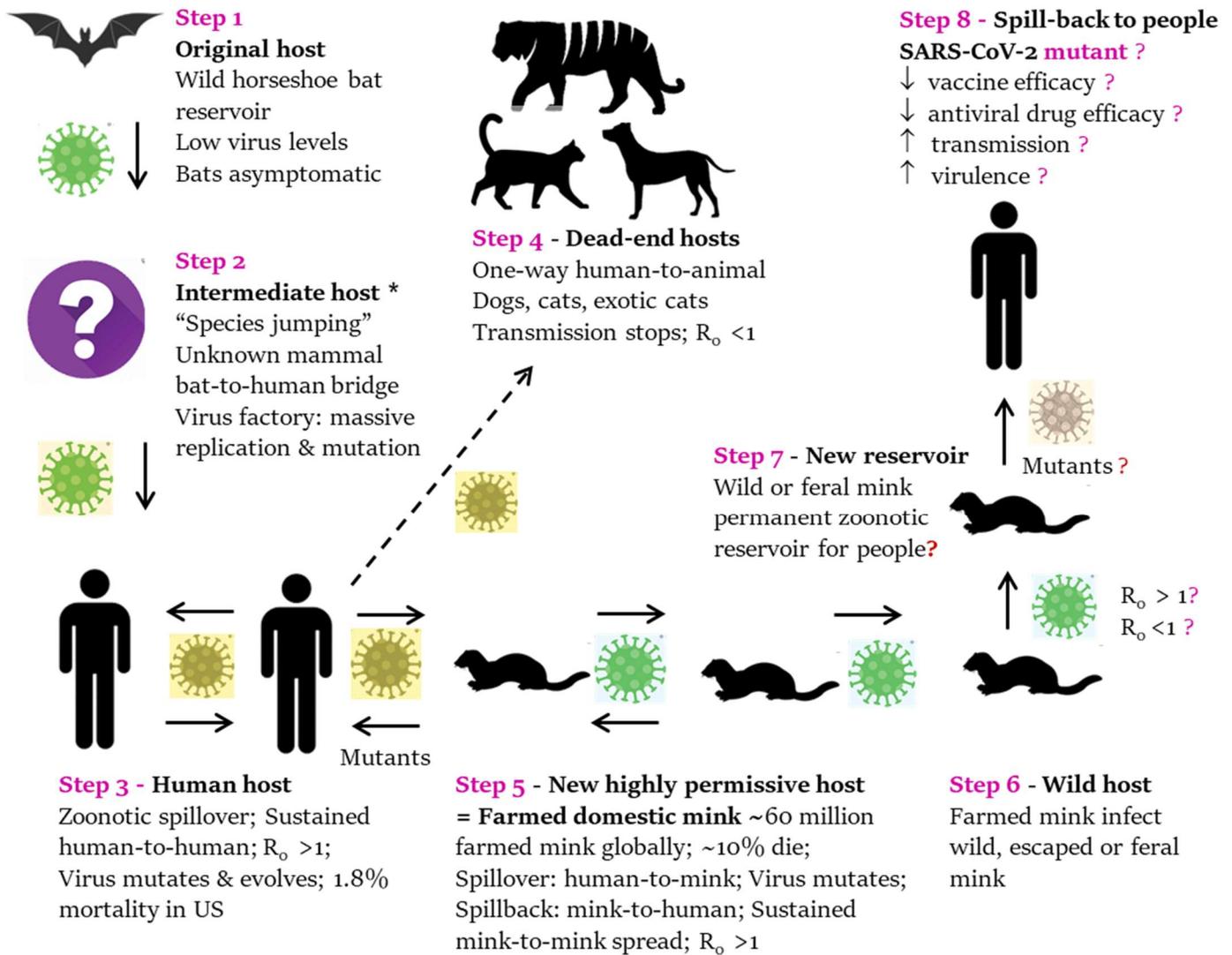
The scientific consensus is that at least the RNA backbone of the SARS-2 virus came from horseshoe bats in China's southern Yunnan Province. Most scientists believe SARS-CoV-2 was not transmitted directly from bats to humans but went through an intermediate animal, either in the wild or in a lab.

Problems with the Shi Zhengli (2021) and the WHO (2021) theory that mink are the intermediate natural zoonotic hosts between bats and people include (Everington 2021):

- Lack of bats or mink in Wuhan's infamous wet market in fall 2019
- Lack of mink in Yunnan in southern China; mink are raised in China's cold northeast more than 900 km from Wuhan and over 2,700 km from Yunnan
- Absence of horseshoe bats (the presumed original bat host genus) in northeastern China

Surprisingly, there are no reported SARS-CoV-2 outbreaks among the 3,000 to 8,000 Chinese mink farms whereas farms across Europe, the U.S., and Canada collectively saw hundreds of farms infected. This is despite the many mink farming commercial links between industry professionals all over the world with the Chinese, especially in North America, northern Europe, and Italy (Faure & Sciana 2021). We must question whether China’s mink farms and government are conducting reliable reporting and surveillance (Corporate Watch 2021).

**Figure 4 - SARS-CoV-2 zoonotic transmission chain: bats, primates & carnivores**



\* Pangolin & mink are candidates  
 $R_0$  = No. of 2° infections per 1° infection

## **5. Reason #5 - Mink SARS-CoV-2 mutants infecting people may evade vaccines or be more virulent or contagious.**

It is fundamental in viral evolution that a virus will change over time and accumulate mutations in their RNA genome that sometimes lead to amino acid substitutions in their proteins. A particular concern is merited when viruses pass between species, including humans and animals (“inter-species jumping”).

SARS-CoV-2 has an inherently high point RNA mutation rate. As RNA viruses, they encode an RNA-dependent RNA polymerase (RdRp) to catalyze the production of new viral RNA. When the viral RNA is replicated, polymerase fidelity errors occur. *RNA polymerase fidelity is diminished in alternative host cell backgrounds and/or virus growth in periods of ecologic stress* (Brüssow 2021). Thus mink infections, as an alternative and distressed host, are mutation prone compared to people (Ferri 2021).

SARS-CoV-2 currently has ~12,700 identified RNA mutations, a number that increases daily (Velázquez 2021). At least 2,737 mutations have been identified in the S (spike) gene of SARS-CoV-2 giving rise to 1,133 amino acid changes, including 171 substitutions in the receptor-binding domains (RBD) (Brüssow 2021).

A group of coronaviruses with the same inherited set of distinctive mutations is called a variant. For example, Cluster 5 is a multi-mutated mink-associated SARS-CoV-2 variant. For the first time in history, next-generation sequencing has permitted near real-time detection of genetic variants as they appear in viral populations during the unfolding COVID-19 pandemic (Brüssow 2021).

While mutations may and do occur anywhere across the entire 30,000 RNA sequences of the SARS-CoV-2 genome, those in the receptor-binding domain (RBD) of the spike protein are most clinically and epidemiologically relevant. This is because the RBD structure determines if and how strong the virus will bind to a human (or mink) cell receptor i.e. angiotensin-converting enzyme 2 (ACE2) (*Figure 5*).

### **A. Diversity in SARS-CoV-2: mutation and recombination**

The SARS-CoV-2 RNA genome (genetic blueprint) is composed of one strand of 30,000 nucleotides (nt), the basic structural unit of nucleic acids. These 30,000 “letters” spell out the sequences for 29 different genes.

- This is one of the largest RNA viruses. In comparison with other single-stranded RNA viruses, HIV is about 10 Kb; influenza is about 13.5 Kb bases.
- In contrast, human DNA is double-stranded, 3.2 billion bases long, and codes for 30,000 genes. Thus, the human genome is 107,000X longer than the SARS-CoV-2 genome.
- The closest known virus to SARS-CoV-2 is from a Chinese horseshoe bat virus which is 96% identical. However, a 4% sequence difference (>1200 bp) would indicate 20 to 50 years of evolutionary separation from SARS-CoV-2, making this bat isolate an unlikely direct source for the COVID-19 pandemic.

SARS-CoV-2 constantly mutates. During replication and multiplying, it copies its genetic material and, in doing so, sometimes makes errors or mutations. Its genome is constantly modified with three kinds of consequences:

- **Neutral:** The mutations have no “observable” consequences: they do not modify the capacities of the virus, which continues to be transmitted in the same way, to infect the same age groups, to cause symptoms of similar severity, etc. to those generated by unmutated viruses. Neutral mutations are transmitted randomly since they offer no particular advantage to the virus that carries them.
- **Deleterious:** Viruses that carry these mutations suffer a competitive disadvantage compared to others (e.g. they are transmitted less well) and are “*selected-against*”.
- **Beneficial:** RNA or amino acid changes can be advantageous for the virus e.g. by allowing it to be more readily transmitted. This new virus - which one can call a “variant” - may infect more people (or mink) more quickly. It may become the dominant virus in the population. Beneficial mutations are “*selected-for*”.

**Figure 5 - SARS-CoV-2 spike protein binds to host angiotensin-converting enzyme 2 in lungs**

**Spike protein of SARS-CoV-2**

- Receptor binding domain (RBD) on spike protein – where virus docks to host ACE2 protein to enable virus to fuse with, enter and infect lung cells

*Analogy: If ACE2 protein is the door lock then the spike protein RBD is the key that unlocks it*

- COVID-19 vaccines and host immune response to infection make antibodies against the RBD that block virus from binding host cells = “**virus neutralization**”
- RBD mutations reduce vaccine or antibody therapy protection i.e. virus makes a “new key” to enter cells. Antibodies against old RBD may not neutralize mutant

“**Cluster 5**” - Danish mink-variant w/ mutated RBD  
 “**Marseilles-4**” = French mink-variant w/ mutated RBD

**Angiotensin-converting enzyme 2 (ACE2) receptor on mink & human lung cells**

- ACE2 is membrane-bound protein common in blood vessels & lungs
- Normal ACE2 function is to lower blood pressure by dilating blood vessels
- Amino acid sequence & 3-D structure of ACE2 binding surface highly variable across animal species & can predict SARS-CoV-2 susceptibility
- SARS-CoV-2 binds w/ high affinity to both mink & human ACE2 even though receptor binding surface w/ several amino acid differences

**Outer lipid bilayer membrane** of lung cell w/ embedded ACE2 protein

*Image modified after Hayashi et al 2020.*

Evolutionary theory predicts that most new viral mutations are deleterious and short-lived, whereas mutations that persist and grow in observed frequency may be selectively neutral or advantageous to viral fitness. Since mutations are stochastic, chance-driven processes, they will occur more frequently where many people (or mink) are infected (hotspots) because the virus is replicating more

frequently than in non-hotspot areas. *Mink farms are SARS-CoV-2 hotspots*. While some mutations arise from simple polymerase fidelity errors, other mutations arise via a more directed response to altered selective pressures on the viral genome (Graham & Baric 2010).

*In vitro* studies have estimated SARS-CoV-2 nucleotide substitution (mutation) rates over most genome regions, as  $3.5 \times 10^{-4}$  substitutions per site per year or  $10^{-3}$  to  $10^{-5}$  mutations per nucleotide (nt) per replication cycle. In infected humans, SARS-CoV-2 mutates approximately every 11-15 days, about half of the rate of influenza (flu) and a quarter of HIV rates (Velázquez 2021). The high inherent SARS-CoV-2 mutation rate combined with a liberal capacity for recombination (creating chimeric viruses when the same host cell is infected with more than one virus strain) allows them to achieve rapid adaptation to new hosts and novel ecological niches (Wong et al 2019).

**B. Mink-associated SARS-CoV-2 variants** - When thousands of fur farm mink are infected, many clinically ill with high viral loads, virus mutation (and even recombination) opportunities are enormous, even likely. The virus appears to evolve at a faster rate in mink than in humans possibly due to the phenomenon of host adaptation (Oude Munnink et al 2021).

Two SARS-CoV-2 mink-associated mutant variants affecting the critical receptor-binding domain of the viral spike protein (the target of all three U.S. vaccines), emerged in 2020: *the Danish “Cluster 5”* (Larson et al 2021) and *the French “Marseille-4”* strains (Fournier et al 2021). Cluster 5 harbors a 2-amino acid deletion and four amino acid mutations (including Y453F, a total of five). Marseille-4 harbors 13 hallmark mutations (including Y453F). Thousands of people were infected by these two mink mutants.

Both the mink Cluster 5 and Marseille-4 variants possess the *hallmark mink-marker Y453F* mutation of the virus spike protein. The Y453F was first found in mink in the Netherlands in April 2020 and Denmark in June 2020. It was later detected sporadically in Russian, South African, Swiss, and U.S. sequences with no link to Denmark and the Netherlands. Afterward, there was a rapid expansion of this mutation in human sample sequences from Denmark. Y453F also occurred in Utah, a top U.S. mink-producing state that was experiencing a SARS-CoV-2 outbreak on mink farms at the same time.

Fearful of seeing SARS-CoV-2 mink-adapted and selected variants such as “Cluster 5” spread more easily among people, to be more deadly, to harm the deployment of anti-COVID-19 vaccines, or to spread to escaped mink, the Danish Government decided to cull their entire 17 million farmed mink population in November 2020. Several countries (Spain, the Netherlands, and France) also ordered the destruction of mink colonies infected with SARS-CoV-2 (Fenollar et al 2021).

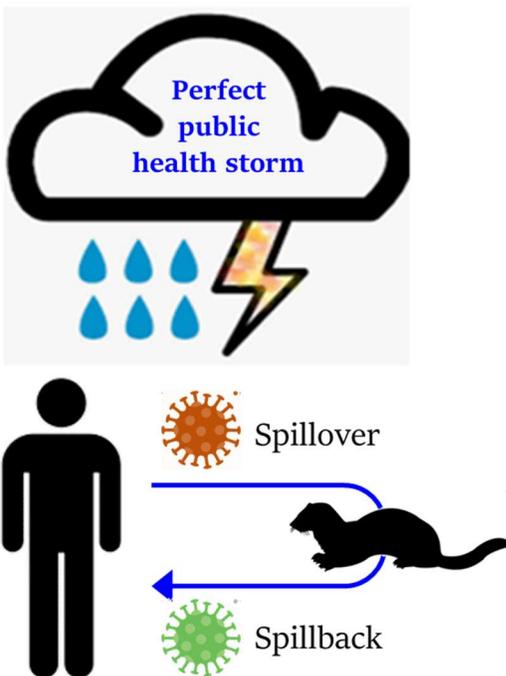
Researchers in Canada discovered two novel variants in SARS-CoV-2 gene sequences collected from Wisconsin and Michigan mink in the U.S. in October 2020 (Cai & Cai 2021). The team identified a two-mutation (N501T-G142D) variant and a three-mutation (N501T-G142D-F486L) variant in the SARS-CoV-2 spike protein - the main structure the virus uses to bind to and infect cells (Robertson 2021).

In essence, the SARS-CoV-2 mutates in mink and people to create new virus variants which may displace, due to evolutionary pressure, previously circulating viruses resulting in loss of vaccine protection, greater transmission, or more severe illness, a phenomenon called “*mutational escape*”.

- Regarding the COVID-19 spike mutations in mink, the *European Centre for Disease Control* (2020) stated: “As a consequence, the evolution of viruses with increasing changes in functional domains

of the S (spike) protein could affect treatment, certain diagnostic tests, and virus antigenicity. It could also have an impact on the effectiveness of developed vaccine candidates, and possibly require them to be updated”.

- *Bayarri-Olmos and colleagues (2021)* demonstrated that the Cluster-5 variant has a mutation (Y453F) in the RBD which is directly involved in the interaction of the virus with the host cell receptor and “... binds the human ACE-2 receptor with a four-fold higher affinity compared to the original (Wuhan) strain suggesting an enhanced transmission capacity and a possible challenge for viral control. These results also indicate that the rise in frequency of the Cluster-five variant in mink farms might be a result of the fitness advantage conferred by the receptor adaptation rather than evading immune responses.”
- *Green & Cladi 2021*: “Could human SARS-CoV-2 re-enter other animal species and - as seems to have happened with the bat and the pangolin - encounter and combine with other animal coronaviruses to create yet more variants, some of which might prove to be dangerous to humans? This is not an outlandish idea—events of this type happen all the time with influenza and have considerable proven potential to damage human health. There have already been suspicions about SARS-CoV-2 variants from mink... SARS-CoV-2 is a clear and present danger. All things are possible, and no possibilities can be discounted without sufficient evidence. Engaging in the process of blue-sky thinking is a long and tough road, but it has to be followed if the human race wants to get ahead of the COVID-19 curve, and for maximum chances of success, the effort undoubtedly has to be international and inclusively worldwide.”



**Box 2 - Spillover, spillback and the perfect public health storm in farmed mink.**

- SARS-CoV-2 tends to mutate and evolve quicker when it jumps to a new host species (spillover or cross-species spread)
- Mutation rates are also highest in hosts in which
  - many individuals become infected e.g. large mink farms with many thousands of densely crowded animals
  - virus replicates to high levels (high viral loads)
  - virus sickens and kills i.e. humans and mink.
- Mink are unique in that after acquiring SARS-CoV-2 from a person (spillover), they can transmit the virus back to people (spillback or reverse zoonosis), sometimes as a mutated virus variant of public health concern

Because of the large mink populations on farms, high infection rates (>90%) and high within-mink viral loads, SARS-CoV-2 frequently mutates in the mink and is then spilled back to people.

In Denmark and the Netherlands, the *spike protein Y453F mutation* was identified as a solid epidemiological marker of a SARS-CoV-2 strain that mutated in mink, as this mutation does not occur

during human infections. The Y453F mutation increases the binding affinity of the virus to the mink ACE2, and thus represents an adaptive response. Because the Y453F mutation occurs in the receptor-binding domain of the spike protein, this mutation is also highly relevant for public health as, for example, it reduces antibody-mediated neutralization of the virus. Please see Supplement 4 for more detailed information on the Y453F and other mink mutations.

Figure 6A describes the chain of events of SARS-CoV-2 outbreaks on mink farms based on outbreak investigations using molecular and field observations in Denmark and the Netherlands. Infected workers introduce the virus onto farms, mink become rapidly infected and spread infection throughout the mink population over a one-to-two week period and then spill-back mutated virus to people.

Figure 6A - Chronology of a typical mink outbreak of SARS-CoV-2: spill-over and spill-back

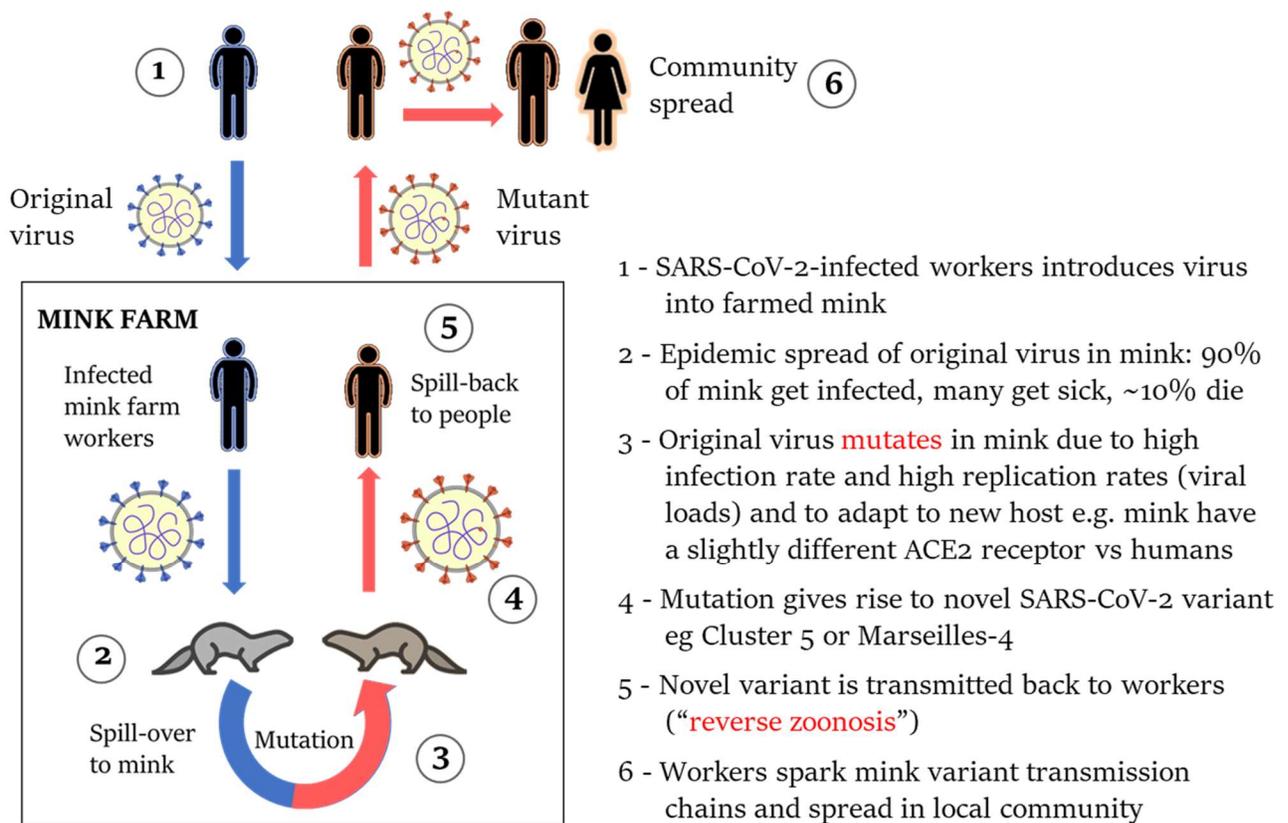


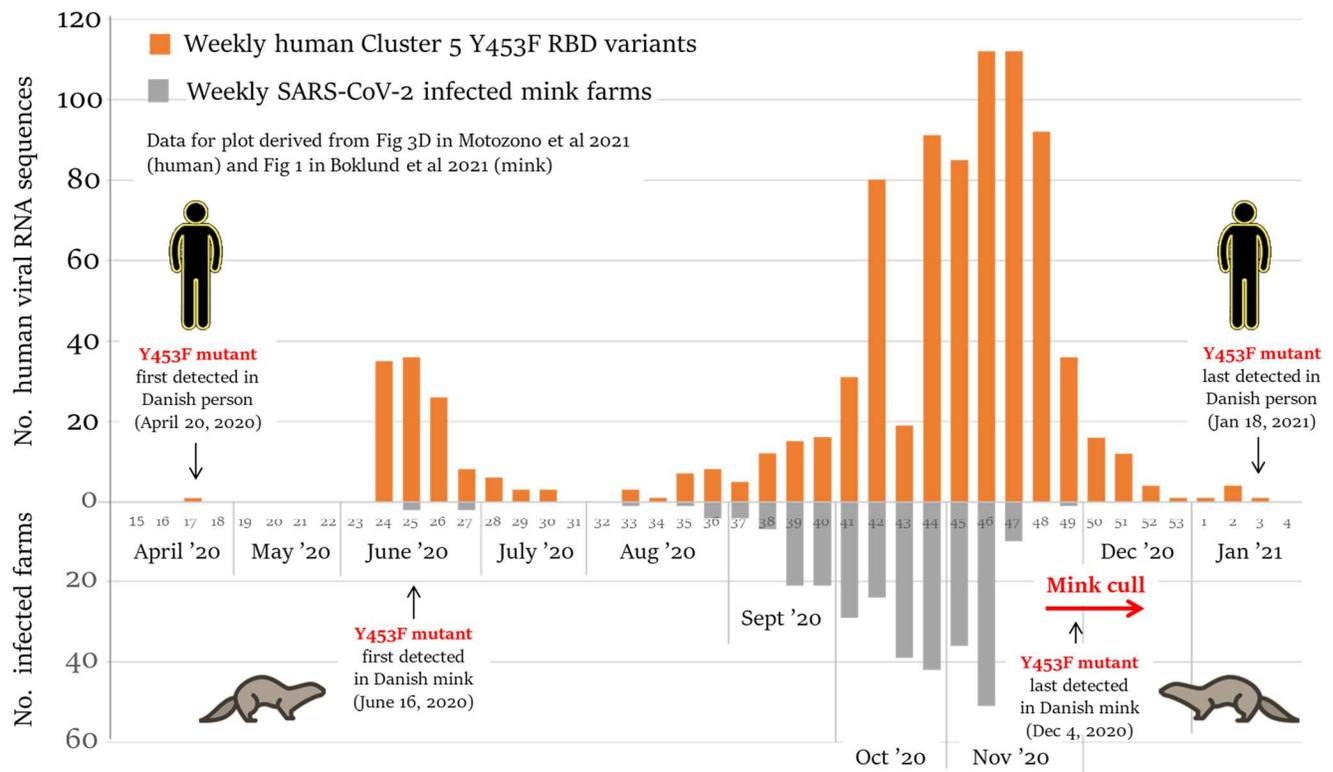
Figure 6B shows the mink-associated SARS-CoV-2 Cluster 5 epidemic curves (cases over time) for 915 people and on 290 mink farms in Denmark in summer and fall 2020. (The Cluster 5 RBD mutant is also called Y453F and B.1.1.298).

The mink cull is rightly credited directly with the rapid extermination of Cluster 5 as Figure 6B clearly shows. It was almost certainly the correct call based on public health risk. Please note:

- (1) The similar steep upward course of both epidemic curves in late summer 2020;

- (2) The precipitous drop in human cases (which had been steadily rising) after the government-mandated nationwide farmed mink cull in November 2020. Cluster 5 went extinct in Denmark by late January 2021.
- (3) The mink mutant was first detected in people in April 2020, two months before the surprising (at that time) farmed mink detection. This suggests that farmed mink had already been infected by workers with a non-mutant SARS-CoV-2 strain and spilled a mutant strain quickly back to people. (Recall that April 2020 was still very early in the COVID-19 pandemic. The first known diagnosis of human COVID-19 in Denmark was on Feb 27, 2020).
- (4) Only a small portion of SARS-CoV-2 are RNA sequenced. Therefore, the Cluster 5 epidemic in 915 people is certainly an underestimate of the epidemic's true size.

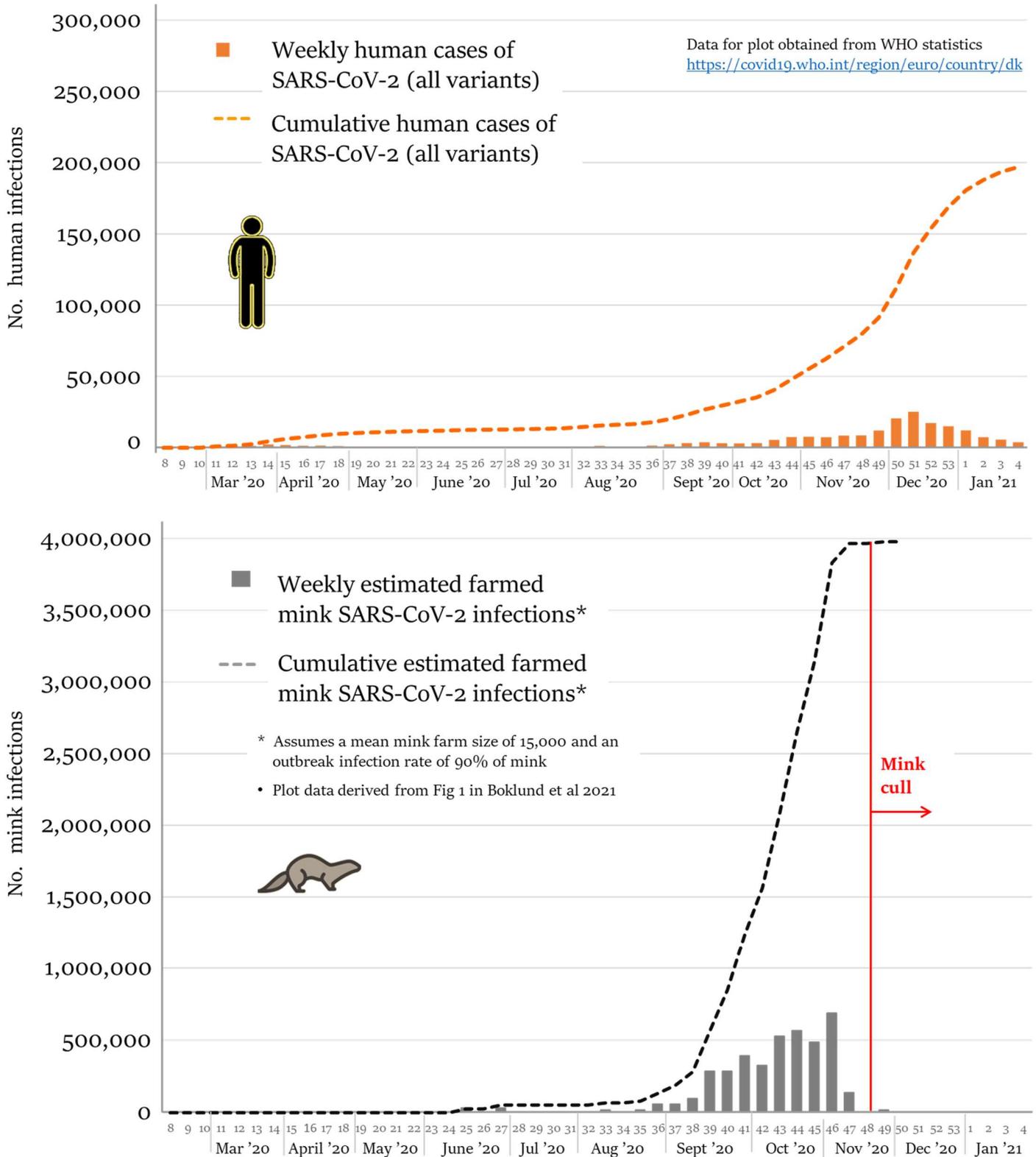
**Figure 6B - Epidemic curves for SARS-CoV-2 Cluster 5 (Y453F) receptor-binding domain mutant variant in 915 people and 290 mink farms in Denmark 2020-21.** The 290 mink farms held ~4.35 million mink (assuming a mean of 15,000 mink per farm), of which an estimated 90% (3.92 million) were infected.



The decision to cull the entire farmed mink population of Denmark in November 2020 was a legal, policy, and public health controversy that led to the resignation of their Minister of Agriculture. Understandably, there were large protests by mink farmers (<https://www.youtube.com/watch?v=dlrgCfRQ4Fk>). However, at the time of Denmark's government's decision to cull their 17 million strong national mink herd in early November 2020, Denmark's human population of 5.8 million was outnumbered 3:1 by its farmed mink.

As shown in **Figure 6C** (upper panel), Denmark had about *91,000 cumulative confirmed cases of human COVID-19* at the end of November 2020, with rapid exponential growth in human infections. At that same time, there were an estimated cumulative *four million infected farmed mink*. New farms were also becoming rapidly infected **Figure 6B** (bottom) and **Figure 6C** (lower panel). Even though Denmark's mink farms were mostly located in rural North Jutland away from urban population centers, this still put strong SARS-CoV-2 epidemiologic force-of-infection pressure on people from mink especially in light of the discovery of mutant mink RBD variants.

**Figure 6C - Weekly and cumulative infections of SARS-CoV-2 in humans (official) and mink (estimated) in Denmark from February 2020 through January 2021.** Please note that the y-axis scales are ten-fold different in mink vs. human infections so the difference between human and mink epidemiologic force-of-infection is 10-fold greater than the plots show.



**C. The public health impact of mink SARS-CoV-2 spike protein variants.** We identified 16 studies that investigated the biological and epidemiologic properties of mutant mink variants. The focus in most studies was the Danish Cluster 5 variant in general and the Y453F RBD mutation in particular. Mink variants were usually compared with the original 2019 human Wuhan isolate (the “wild type”, WT) which is considered the unmutated reference strain. (This wild-type virus was used to design all human vaccines.) A summary of the findings of these 16 studies is shown in **Table 3**. Specific study details in methods, results, and interpretation are found in *Supplement 4*.

Approaches used to assess SARS-CoV-2 mink variant public health risk included:

- *In silico* - virus whole genome RNA sequence: look for changes in spike protein RBD or RBM
- *In vitro* - virus growth kinetics e.g. titer and growth rate in cultured human cell lines
- Biochemistry - virus binding affinity to human and mink ACE2 receptor
- Virus neutralization - by mAbs, convalescent sera, and plasma from vaccinated persons

The focus of several studies was to assess mink variant (1) susceptibility to being neutralized by antibodies from wild-type viruses and (2) virus binding affinity (chemical bond strength) to the human ACE2 receptor. Reduced neutralization and stronger bonds usually correlate with greater virus infectivity and transmission risk. Most studies report that the Y453F mutation resulted in reduced antibody-mediated protection vs. wild-type virus and higher affinity binding to the human ACE2 cellular receptor. The mink mutants were “worse” or the same as the wild-type virus for all properties measured except one: mink Y453F mutants showed less *in vitro* infectivity in two reports.

The *virus neutralization assay* is an *in vitro* serological test to detect the presence and amount (titer) of functional antibodies to prevent a virus from infecting host cells (Focosi & Maggi). The virus is “neutralized” by antibodies if it cannot bind to the ACE2 host cell receptor. (By analogy, if the virus spike RBD is the “key” and ACE2 is the “lock”, in neutralization the “key” is covered with tape i.e. the RBD key is covered in antibodies so it cannot “unlock” the ACE2). Binding of neutralizing antibodies to a virus variant (“mutant”) may differ from their binding to the original (“wild type, WT) virus.

**Figure 7A** diagrams a virus neutralization assay for a mink mutant vs. wild type SARS-CoV-2.

A rigorous study by Hoffman and colleagues (2021) investigated the *in vitro* ability of convalescent plasma from recovered COVID-19 patients and two FDA-approved therapeutic monoclonal antibodies (mAb) to neutralize the Cluster 5/Y453F mink variant. In a series of experiments, they showed (**Figure 7B**) that SARS-CoV-2 Cluster 5/Y453F mutations from mink:

- (1) Generally reduce antibody-mediated neutralization (*bad public health outcome*)
- (2) Permit escape from the therapeutic monoclonal antibody (mAb) Casirivmab (*bad outcome for COVID-19 patients*)
- (3) Allow evasion of antibodies induced by human SARS-CoV-2 infections i.e. convalescent plasma from a recovered COVID-19 patient is less effective in killing the virus (*bad public health outcome*)

On a more optimistic side, Hoffmann’s study found:

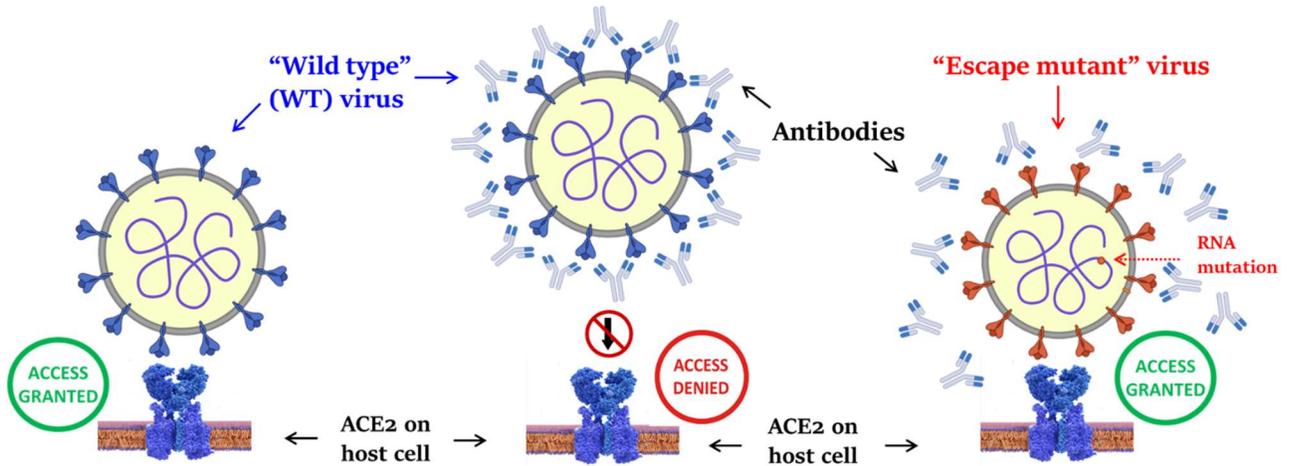
- (4) Entry inhibitors (drugs) under clinical evaluation block mink spike proteins, meaning the drugs work as expected against the mink variant.

- (5) The mink virus does not appear to increase virus entry into human cells *in vitro* i.e. no increase in infectivity vs. wild type.
- (6) The mink virus does not reduce virus neutralization with the therapeutic mAb Imdevimab i.e. this mAb still works as desired for therapy (unlike therapeutic mAb Casirivimab).

**Table 3 - Public health relevance of mink SARS-CoV-2 variant mutants: findings from 17 studies.** Red font = worse for public health vs. wild type virus; Blue font = better for public health vs. wild type virus; Green font = same risk (or benefit) as wild-type virus

Outcome metric	Evidence	Wuhan non-mutant	Cluster 5 mink mutant	References
Antibody protection after convalescence	<i>In vitro</i>	High	Reduced	Lassaunière et al 2020, 2021; Hoffmann et al 2021; Hayashi et al 2021; Zhang et al 2021; Ren et al 2021
Antibody protection after vaccination	<i>In vitro</i>	High	Mouse model Human mRNA	Bayarri-Olmos et al 2021; Garcia-Beltran et al 2021
Therapeutic monoclonal antibody effectiveness	<i>In vitro</i>	High	Reduced or ineffective e.g. mAb Casirivimab	Hoffmann et al 2021; Tada et al 2021
Binding affinity to host ACE2 receptor	<ul style="list-style-type: none"> <li>○ <i>In vitro</i></li> <li>○ Computational</li> <li>○ <i>In silico</i></li> <li>○ Direct measures</li> </ul>	High	<ul style="list-style-type: none"> <li>○ Higher human</li> <li>○ Higher mink</li> </ul>	Bayarri-Olmos et al 2021; Burkholz et al 2021; Gobeil et al 2021; Hayashi et al 2021; Hoffmann et al 2021; Lassaunière et al 2020, 2021; Motozono et al 2021; Welkers et al 2021; Ren et al 2021
Transmissibility	<ul style="list-style-type: none"> <li>○ Clinical epidemiology</li> <li>○ Statistical models</li> </ul>	Community spread	Higher community spread (most studies)	Fournier et al 2021; Lassaunière et al 2020, 2021; Konishi 2021; Oude Munnick et al 2021;
Virulence	<ul style="list-style-type: none"> <li>○ Clinical epidemiology</li> <li>○ <i>In vitro</i></li> </ul>	Wild type	Same as wild type ↓ infectivity ( <i>in vitro</i> ) ↓ cellular immunity ( <i>in vitro</i> )	Fournier et al 2021; Lassaunière et al 2020, 2021; Hayashi et al 2021; Oude Munnick et al 2021; Zhang et al 2021; Motozono et al 2021
Innate resistance to remdesivir (anti-viral drug)	<i>In silico</i>	Low	Low	Martin et al 2021

**Figure 7A - Wild type (WT) and mutant virus neutralization and host-virus binding**



**A - Immuno-naïve person**

- Virus contacts ACE2
- Spike RBD binds tightly to ACE2
- Virus enters host cells & replicates

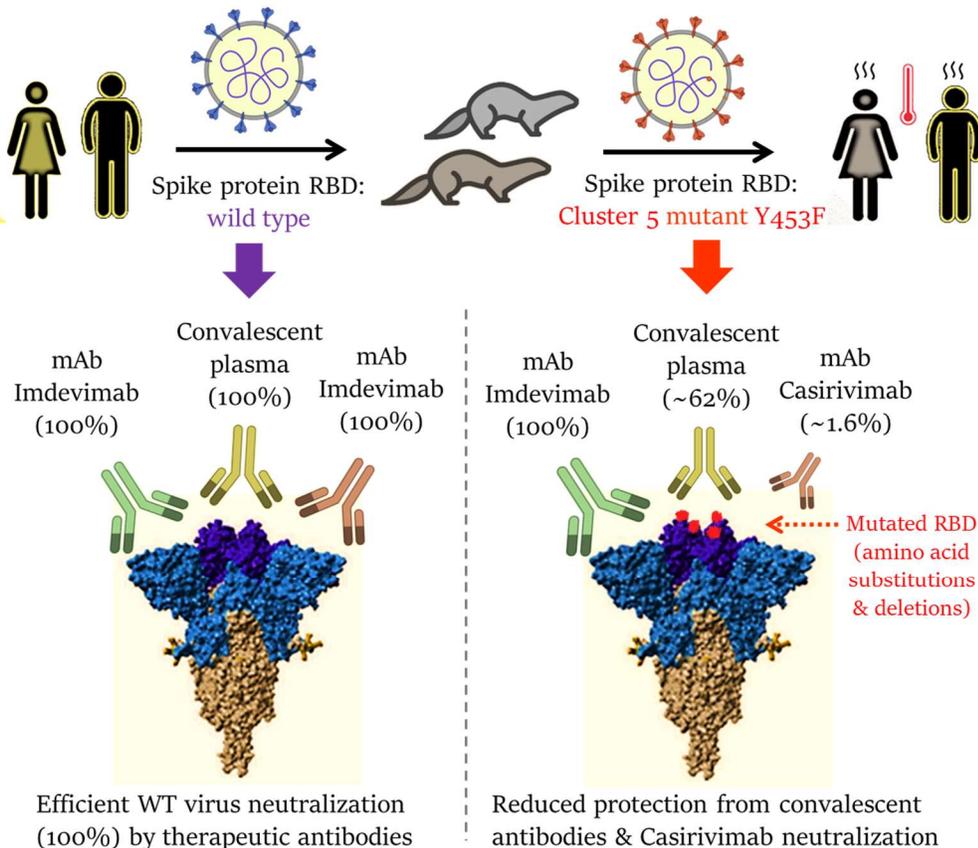
**B - Immuno-competent person**

- Vaccinated or recovered
- Antibodies bind to spike; block RBD
- Virus cannot bind to ACE2

**C - Immune to WT but exposed to mink virus w/ mutated spike RBD**

- Antibodies bind poorly to mutated RBD
- Spike protein RBD binds tightly to ACE2
- Virus enters host cells & replicates

**Figure 7B - Reduced antibody protection against mink SARS-Cov-2 mutant RBD variant. SARS-CoV-2 mutations acquired in mink reduce antibody-mediated virus neutralization**



**Definitions**

**WT** = wild type virus; original unmutated Wuhan virus; used to design vaccines

**RBD** = receptor binding domain; spike protein location that binds to cells; permits host entry

**Y453F** = mink virus variant w/ mutated RBD on spike protein; a Cluster 5 mutation

**mAb** = human monoclonal antibodies used to treat COVID-19

**Convalescent plasma** = blood from SARS-CoV-2 recovered persons

*Modified from Hoffmann et al 2021*

Efficient WT virus neutralization (100%) by therapeutic antibodies

Reduced protection from convalescent antibodies & Casirivimab neutralization

### ***D - Long-term impact escape mutants: SARS-CoV-2 endemicity as series of unfortunate events***

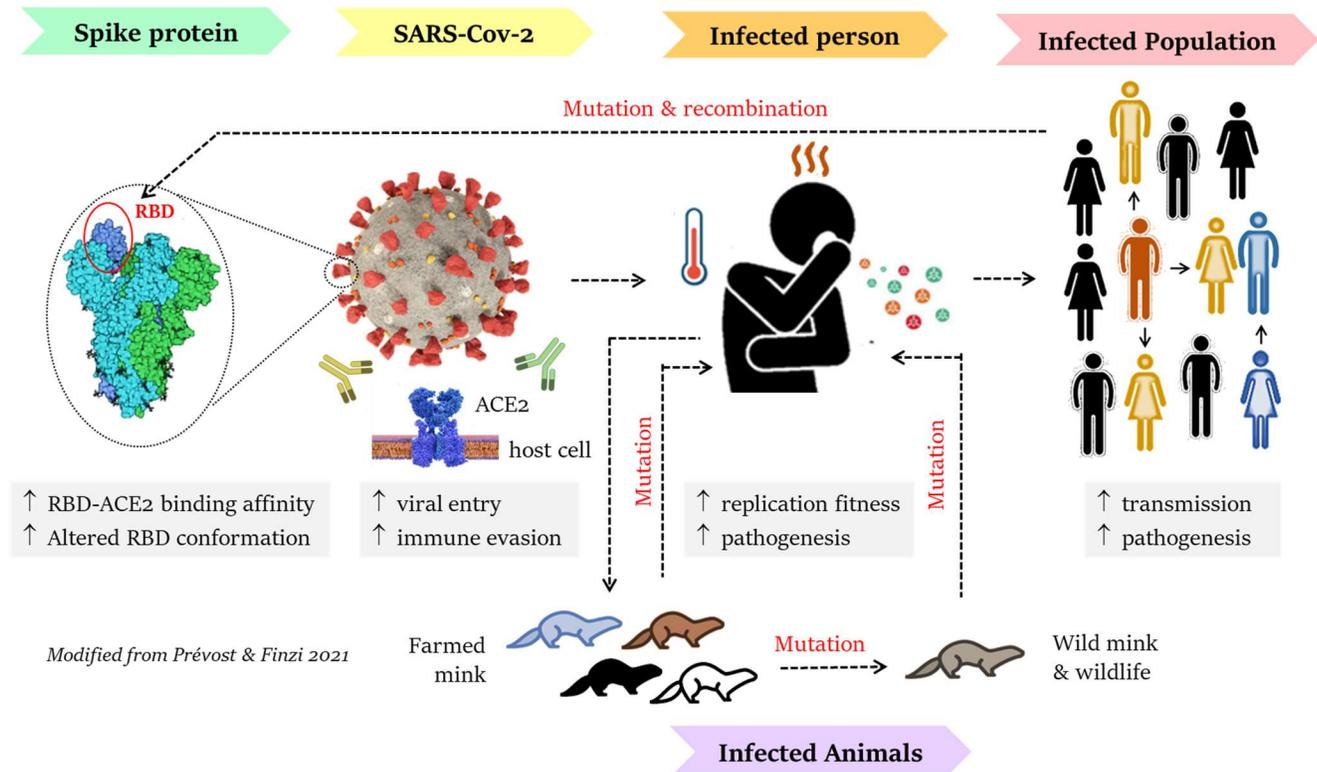
The importance of SARS-CoV-2 escape mutants from natural immunity, from therapeutic antibodies, from vaccines, or drug therapies cannot be overstated whether they originate in humans or mink, or other host animals (Prévost & Finzi 2021; Nikhra 2021). In **Figure 8**, multi-level drivers of escape mutant creation and propagation are proposed. These include:

- *Spike protein especially the receptor-binding domain* - The RBD faces strong selection pressure from host neutralizing antibodies especially in the receptor-binding motif (RBM) resulting in near deterministic eventual emergence of spike escape variants such as mink Cluster 5.
- *The virion* - RBM mutations can increase receptor binding affinity for the host ACE2 receptor or alter its conformational state to ease viral entry (as in mink Cluster 5). Spike antigenicity changes enable immune evasion from humoral antibodies. Due to evolving genomic changes, the virus elicits an erratic and labile host immune response.
- *People* - Viral passage through infected persons, especially those with immunosuppressive conditions, may enhance viral replication fitness and alter viral pathogenesis (Bazykin et al 2021). Human host factors are highly variable and largely uncontrollable.
- *Human populations* - Escape mutants could increase viral transmission and even fatality rates. There already is evidence that herd immunity against SARS-CoV-2 may remain a myth, with individual immunity being labile and waning after 6-8 months and booster doses of updated vaccine to be required at regular intervals. When an increasing portion of a population gets infected or vaccinated, the number of people with neutralizing antibodies against the circulating viruses will increase. This generates strong selection pressure for immune escape mutants and could drive emergence and prevalence increase of spike variants. (The same phenomena will occur with farmed mink vaccination.)
- *Farmed and wild mink or wildlife* - spill-over to and spill-back from farmed and wild mink raise risks of generating new escape variants due to the need of the virus to adapt to a new host and new environment. Wildlife reservoirs also add to the risk for SARS-CoV-2 recombination i.e. the same host cell is infected by more than one viral strain that then creates novel chimeric viruses, a potentially rapid change in the virus of much greater magnitude than mutation (Prince et al 2021).

*Nikhra 2021*: “It is likely that the SARS-CoV-2 will not be eradicated but become endemic and continue to circulate and cause infections in pockets of the global populations for years to come. It may evolve into more transmissible and virulent forms with novel mutations and variants, and associated factors may worsen the overall scenario with involvement of newer population groups and world regions ...

The unabated prevalence increases risk of mutations, as the virus has more chances to mutate. Further, in areas where the incidence rates are high, selection pressures favour the emergence of variants that evade neutralising antibodies. Furthermore, as population groups receive vaccination, immune pressure is conjectured to facilitate and speed up the emergence of such variants by selecting for escape mutants. In due course, these selected variants would replace previous versions of the virus propelling the pandemic or the endemic disease later on.”

**Figure 8 - SARS-CoV-2 escape mutants and COVID-19 endemicity.** There are multi-level drivers of eventual permanent SARS-CoV-2 establishment via escape mutants. Drivers range from the RBD on the spike protein molecule, to the virion (infectious virus particle), to the individual infected person, to the human population, and animal (e.g. mink) populations.



In total, the epidemiological drivers shown in **Figure 8** may lead to (1) persistence of the SARS-CoV-2 or its mutant viral progeny and (2) endemicity of the disease interspersed by periodic outbreaks and re-emergence. Farmed mink can only contribute to these undesirable outcomes.

American author and clergyman Edward Everett Hale said, “I cannot do everything, but still I can do something.” Similarly, U.S. President Calvin Coolidge said, “We cannot do everything at once, but we can do something at once.” They were both correct.

The “something” we can do is ban mink farming. There were compelling reasons to oppose fur farming grounded in the inhumane nature of the business enterprise and limited geographic and high-income export market of the product before the COVID-19 pandemic. Now considerable public health risk from zoonotic SARS-CoV-2 in mink farms makes the elimination of mink farming even more pressing.

Just as SARS-CoV-2 initially emerged in China in late 2019 as a result of coronavirus mutations and recombinations in (unknown) animals, the present and future risk from SARS-CoV-2 mostly comes from viral mutations and recombination that produce vaccine or therapy escape mutants. As shown in **Table 4**, the elimination of mink farming is something we can do to decrease the risk of dangerous escape mutants from mink that will jeopardize our individual health and community immunity from vaccination or natural exposure to the virus.

**Table 4 - Exiting the path to SARS-CoV-2 endemicity: decreasing the public health risk of SARS-CoV-2 escape mutants by banning mink farming**

Driver	Problem	An issue in farmed mink?	Will banning farmed mink reduce risk?
Public policy: health, agriculture & wildlife	Lack of preventive control measures	Yes - farms largely unregulated pre-COVID-19	<b>Yes</b>
Unreliable host immune response to infection or vaccine	<ul style="list-style-type: none"> <li>○ Labile immunity</li> <li>○ Low herd immunity</li> <li>○ High <math>R_0</math><sup>1,2</sup></li> </ul>	<ul style="list-style-type: none"> <li>○ Yes - immunity lost in &lt;3 mo<sup>3</sup></li> <li>○ Yes - immunity lost in &lt;3 mo<sup>3</sup></li> <li>○ Yes<sup>2</sup></li> </ul>	<b>Yes</b>
Virus “cunning”	Immune escape and emergence of variants	Yes - documented e.g. Cluster 5 and Marseille-4	<b>Yes</b>
Virus adaptability	Persistence in wild animal reservoir	Yes - farmed mink virus spill-over to wildlife reservoir likely (WHO)	<b>Yes</b>

<sup>1</sup>  $R_0$  = basic reproduction number = mean no. of secondary cases of infection per primary infection.  $R_0$  for SARS-CoV-2 in people is estimated to range from 3 to 7 depending on local epidemiologic conditions.

<sup>2</sup>  $R_0$  has not been formally calculated in farmed mink. However, it must be empirically high based on many outbreak investigations.

<sup>3</sup> *Rasmussen et al 2021*: On a large Danish mink farm in 2020, 100% of mink were infected, all recovered, then 75% were re-infected <3 mo later with both outbreaks caused by very similar SARS-CoV-2 strains

**6. Reason #6 - Farmed mink are raised in high stress-low welfare conditions that maximize chances for dangerous SARS-CoV-2 infections and mutations.**

*If SARS-CoV-2 could design its perfect habitat, it might closely resemble a mink ranch: a pan-susceptible, highly stressed, immuno-suppressed inbred host, fed an unnatural diet, kept in tiny cages, and co-housed with thousands of conspecifics. This environment maximizes chances for infections and mutations. Wild mink are predatory, solitary, semi-aquatic wide-ranging animals that are biologically unsuitable for industrial animal farming conditions (Xia et al 2020).*

Mink are not just more susceptible to COVID-19 on a molecular level, they also get sick more than other animals because of their high density, high-stress farm environment to which they are genetically, behaviorally, and physiologically mal-adapted. *Farmed mink welfare and SARS-CoV-2 risk cannot be disentangled or divorced from one another, and in this sense, SARS-CoV-2 is an anthropogenic disease of fur production.*

*Note: Please see Supplement 2 for detailed background information describing differences in biology and lifestyles of free-ranging wild mink versus captive farmed mink and their relationship to COVID-19 risk.*

- Like other animals subjected to industrial farming conditions, the life of a farmed mink is, to paraphrase Hobbes, “poor, nasty, brutish, and short.” But public health risks from mink make them especially unsuited for industrialized farming. Even before COVID-19, farmed mink were infamous for their susceptibility to epidemics including zoonotic influenza H5:N1 (Fenollar et al, 2021).
- As solitary anti-social animals that *naturally social distance*, the mink immune system evolved to deal with infrequent pathogen encounters and rare contact with other mink. The industrial conditions of crowding thousands of mink in close proximity that make it easy for people to raise mink also make it easy for pathogens like SARS-CoV-2 to prosper.
- These anti-social animals are forced to live in close sight, smell, and sound of thousands of other mink. They are often forced to live several to a small cage.
- Keeping solitary and socially antagonistic carnivores in close-confinement in small cages is a prescription for intraspecific aggression, biting, and even cannibalism. Mink are not herd or flock animals, and the presence of a conspecific may trigger territorialism and violent attacks. Weaker mink cannot escape so fighting often results in chewing off of ears, tails, and even evisceration (e.g. <https://youtu.be/meFB3EJWj-o> and personal communications with former mink farmers).
- It should not surprise that chronic high anxiety prison-like conditions on mink ranches, where natural instincts are frustrated and suppressed, result in abnormal behaviors. These include self-mutilation, cannibalism, infanticide, and stereotypical behaviors e.g. pacing or circling, bar chewing, etc. (Jespersen et al 2016). These behaviors are not expressed by wild mink as they would be detrimental to survival and reproduction (Dunstone 1993).
- The distress manifest as abnormal behaviors inflates infectious disease risk *invisibly* by suppressing immunity (Broom & Kirkden 2004; Early et al 2010).
- Reduced genetic diversity (inbreeding) to achieve desirable fur properties (e.g. coat color), selective breeding for large body size, large litters, and fast growth as well as abnormal unnatural diet also factor in farmed mink susceptibility to COVID-19 and other diseases.
- SARS-CoV-2 infected mink ranches are true potential “*super-spreader*” sites or *hotspots*. An epidemic will usually run its course on a mink farm in two weeks or less (Golden 2021). A typical U.S. mink farm has about 15,000 animals. In an outbreak, ~90% of mink are infected and ~10% die.
- Using daily tissue-specific quantitative viral loads from experimentally challenged rhesus monkeys (Sender et al 2020) adjusted for the smaller size of mink, we estimate that an infected mink farm of 10,000 animals sheds more than a billion infectious SARS-CoV-2 particles per day. This is enough to infect 10 million people per day at an infectious dose of 100 virions. This huge communal mink viral load and the massive SARS-CoV-2 replication it represents is a mother of mutant mink variants and virus mutational escapees from vaccines and therapeutics.

*Fenollar 2021*: “Interestingly, many emerging infectious diseases reported in mink have high zoonotic potential. It seems that farmed mink are susceptible to the infections of different vertebrates, including birds (Newcastle disease, avian influenza H5:N1); dogs (distemper), pork (pseudorabies herpes virus), and humans (influenza, SARS-COV-2).”

According to the website “Truth About Fur” (<https://www.truthaboutfur.com>) sponsored by the Fur Council of Canada, (FCC) mink farming was pioneered in the U.S. more than 150 years ago during the Civil War at Lake Casadacka, New York to provide needed warm clothing in harsh winters for soldiers. The FCC claim that after 150 generations, farmed mink can be considered a domesticated animal. Farmed mink are about double the size of wild mink and generally tamer.

However, domestic cattle, sheep, goats, and swine have been under domestication for 8,000 to 10,000 years, representing many thousands of generations. Dogs were domesticated 14,000 to 36,000 years ago. Farmed mink are still very early on the path to domestication and retain many of their wild instincts (Schaffner 2021). For example, heavy gloves must be worn when handling farmed mink due to their propensity to bite viciously just as one would expect from a wild predator and not a tame domestic one. Farmed mink remain essentially wild animals (See **Box 3**).



**Box 3 - Farmed mink manual restraint.** Notice (a) heavy leather gloves worn by mink handler during restraint and (b) the anxious angry tense body language and posture and open mouth of the “tame domestic” mink. Many farmed mink exhibit a fearful-aggressive response to humans which is uncharacteristic of truly domestic animals (Kenner 2020).

**7. Reason #7 - Vaccinating mink is not a panacea for high volume-low welfare conditions of fur farms that make mink so vulnerable to disease in the first place.**

HL Mencken said, “For every complex problem there is an answer that is clear, simple, and wrong.” Some veterinarians and the mink industry propose vaccinating mink against COVID-19 to address the public health risk from mink. An experimental mink vaccine made by Zoetis became available in the U.S. in summer 2020 and was used to vaccinate more than 90% of US farmed mink. Russia and Finland have also developed, but not yet deployed, experimental mink vaccines. However, mink SARS-CoV-2 vaccines will not eliminate risk (Weese 2021).

- Vaccines alone have *never eliminated any animal disease*. For example, mink farmers routinely vaccinate against influenza, distemper, *Pseudomonas*, botulism, and mink enteritis virus, yet all of these infectious diseases remain epidemic or endemic risks on mink ranches worldwide (Hildebrandt 2021).
- Vaccines are almost always “*non-sterilizing*” i.e. they may prevent severe clinical disease but usually do not completely prevent infection or transmission (Weese 2021). The U.S. vaccines for mink by Zoetis (Parsippany NJ) and MedGene (abandoned in June 2021; Brookings SD) reportedly use recombinant SARS-CoV-2 spike protein, the same target as in all U.S. human COVID-19 vaccines (Gorman 2021). Therefore, mink vaccination will put additional evolutionary pressure on the COVID-19 virus that may increase the risk of human vaccine failure via mutational escape. The mink vaccine has implications for viral fitness (ability to infect humans and animals), transmissibility, and antigenicity.
- Vaccinating mink *may simply make infected mink harder to detect* as a subclinical disease but maintain their ability to create more virus variants. Vaccination may also interfere with serological monitoring of farms for COVID-19, as vaccine response can appear indistinguishable from infection. For example, this is the reason that foot and mouth disease (FMD) vaccination is banned in U.S. livestock: vaccination would make an FMD outbreak hard to detect by hiding disease symptoms and creating vaccine-seropositive animals indistinguishable from natural FMD infection.
- Even if a vaccine for mink is deployed in 2021, new vaccine formulations will likely *be needed routinely to adjust to new virus variants* that make the original vaccine ineffective (Banerjee et al 2021; Plante et al 2021).
- Some believe a COVID-19 mink vaccine is useful as “management in a bottle”. However, even a good vaccine may fail in a high viral load farmed mink barn filled with highly-stressed, overcrowded immuno-compromised mink biologically maladapted to the mink ranch environment.
- Mink vaccines may be subsidized by the government in 2021. However, mink COVID-19 vaccines are unlikely to be continuously underwritten in the future. Furthermore, testing (as opposed to vaccination) for SARS-CoV-2 is not subsidized in most states. Administering intra-muscular vaccines like the ones people are receiving across the country is expensive and labor-intensive so a mink vaccine would probably need to come in oral, nasal, or aerosol form (Eurogroup for Animals 2021).

#### Box 4 - The simple math of mink farm herd immunity & vaccine protection ... or failure

Mink farmers and the mink industry in the U.S. have put their SARS-CoV-2 prevention and control hopes and dreams on a mink vaccine. Two commercial U.S. mink vaccines are expected to be released in summer 2020 pending approval by the USDA Center for Veterinary Biologics. The state of Oregon mandated that all mink farmers vaccinate their animals before August 2021. However, SARS-CoV-2 biology and farmed mink practices may derail the mink vaccination plan:

- (1) A simple formula allows one to estimate effective vaccine coverage ( $V_c$ ) needed to stop a contagious infection (Fine et al 2011):

$V_c$  = vaccine coverage necessary to stop spread of a contagious infection =  $(1 - 1/R_0)/E$  where:

$R_0$  = basic reproduction number = the average number of secondary cases of infection transmitted by each primary case in a susceptible population

$E$  = vaccine efficacy = the proportion of vaccinated individuals who become immune and non-infectious i.e. unable to transmit the virus. Vaccines in the real world are never 100% efficient due to either imperfections in the immunogenicity of vaccine formulation itself, improper vaccine delivery or storage or due to immuno-non-responsive hosts.

$1 - 1/R_0$  = fraction of individuals needed to be immune in a susceptible population to stop an outbreak

- (2) A recent estimate of  $R_0$  in the U.S. in early 2020 (when the U.S. had no herd immunity to the novel corona virus) is: median  $R_0 = 5.9$  with a 95% confidence interval between 4.7 and 7.5 (Ke et al 2021).

Therefore, for human SARS-CoV-2 assuming a median  $R_0 = 5.9$  and vaccine efficiency ( $E$ ) = 90%:

$V_c = (1-1/5.9)/0.9 = 0.83/.9 = 93%$  (range 87% to 96%).

If this  $R_0$  is correct, the U.S. must maintain a high vaccinated proportion to prevent SARS-2 spread.

- (3) We believe with evidence that SARS-2  $R_0$  in mink is likely (much) higher than human  $R_0$ .

SARS-CoV-2 can infect 90% of mink on a farm in a matter of days because of crowded housing and stressed immune systems, so we can reasonably assume a mink  $R_0$  of 10 and a vaccine efficacy of 80%. We discount mink vaccine efficacy from 90% to 80% due to stress-induced herd immunosuppression.

Therefore, for mink SARS-CoV-2 assuming  $R_0 = 10$  and  $E = 80%$ :

$V_c = (1-1/10)/0.8 = 0.9/0.8 = 113%$  i.e. vaccine coverage must exceed 100% = impossible!

In other words, complete herd immunity is not achievable on mink farms even with a vaccine. SARS-CoV-2 transmission will persist.

- (4) Conclusion - Mink have a high SARS-2  $R_0$  and consequently high herd immunity threshold. Mink vaccines are unlikely to prevent human-to-mink or mink-to-human spread.

- Mink vaccines will probably protect against SARS-2 clinical disease. This and safety are primary outcomes weighed by USDA for approval just as they are for FDA-approval of human vaccines.
- Strong evolutionary pressure means mink vaccine escape mutants will develop sooner rather than later. Human booster shots for virus variants are already being prepared for fall 2021 delivery.
- Rasmussen and colleagues (2021) showed that herd immunity on a commercial mink farm was gone in less 3 months: the mink were re-infected with a near-identical SARS-2 strain. Vaccines are unlikely to perform better than this documented labile natural exposure immunity.

- Rasmussen et al 2021 in Denmark in late 2020 demonstrated clearly and surprisingly that farmed mink can be heavily infected by SARS-CoV-2, seroconvert and then be heavily re-infected less than three months later with essentially the same virus strain. This finding does not bode well for mink individual or herd immunity whether via natural infection or simulated infection (i.e. mink vaccination). From the abstract:

“Mink, on a farm with about 15,000 animals, became infected with SARS-CoV-2 [in Aug 2020]. Over 75% of tested animals were positive for SARS-CoV-2 RNA in throat swabs and 100% of tested animals were seropositive. ... The infected mink recovered and after free-testing of the mink, the animals remained seropositive. During follow-up studies, after a period of more than 2 months without virus detection, over 75% of tested animals scored positive again for SARS-CoV-2 RNA [in Nov 2020]. Whole-genome sequencing showed that the virus circulating during this re-infection was most closely related to the virus identified in the first outbreak on this farm but additional sequence changes had occurred.”

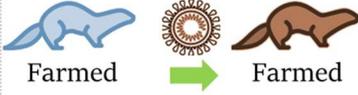
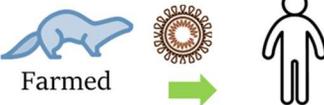
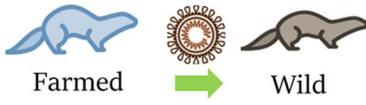
- There are other COVID-19 health economics realities for mink farmers. As *Schlanger (2020)* wrote: “There are no indemnity programs ... If you have a major mortality problem, you’re losing a significant amount of profitability. Then there’s the cost of testing. Sixty-two animal [PCR] tests cost \$3,000, [\$48/test] which is a big deal to a farm that just suffered losses of tens of thousands of dollars,” [Keith] Poulsen said. To avoid further contamination, mink farmers must compost the dead bodies, as well as any used feed and fecal matter. “There’s no money to do that on the federal or state level, so that’s all on the farm”, [said] Keith Poulsen, the director of the Wisconsin Veterinary Diagnostic Laboratory.

## **8. Agreement of our findings with the January 2021 SAR-2 WHO/OIE/FAO report**

Our scientific assessment that European and U.S. farmed mink pose a substantial public health hazard from SARS-CoV-2 agrees with the Food and Agricultural Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO). These three inter-governmental organizations published a tripartite qualitative risk assessment on the impact of SARS-CoV-2 in fur farmed mink on public health, livelihoods, wildlife, and animal welfare in January 2021 for the 36 nations that practice fur farming (WHO/FAO/OIE 2021). A qualitative risk assessment combines the estimation of the likelihood of a hazard with the severity of its consequences.

This qualitative risk assessment was conducted at the regional and national levels and included weighing the overall likelihood of the three consequential adverse events shown in **Table 5**. The assessment for the U.S. was based on: (1) our farmed mink population of 2-3 million animals; (2) moderate mink farming biosecurity practices; (3) the occurrence of more than 21,500 cases of SARS-CoV-2 in farmed mink to date; and (4) the large and diverse populations of eleven wild mustelid species (e.g. mink, badger, weasel, wolverine, otter, etc) across the nation. From these inputs, the likelihood of occurrence in the U.S. for each adverse consequential SARS-CoV-2 event from mink farming was classified as either “*very likely*” or “*likely*” (**Table 5**).

**Table 5 - Likelihood of three adverse and consequential outcomes from SARS-CoV-2 in farmed mink in the U.S.** Based on risk assessment by three international inter-governmental agencies with human health (WHO), animal health (OIE), and food and agriculture (FAO) missions.

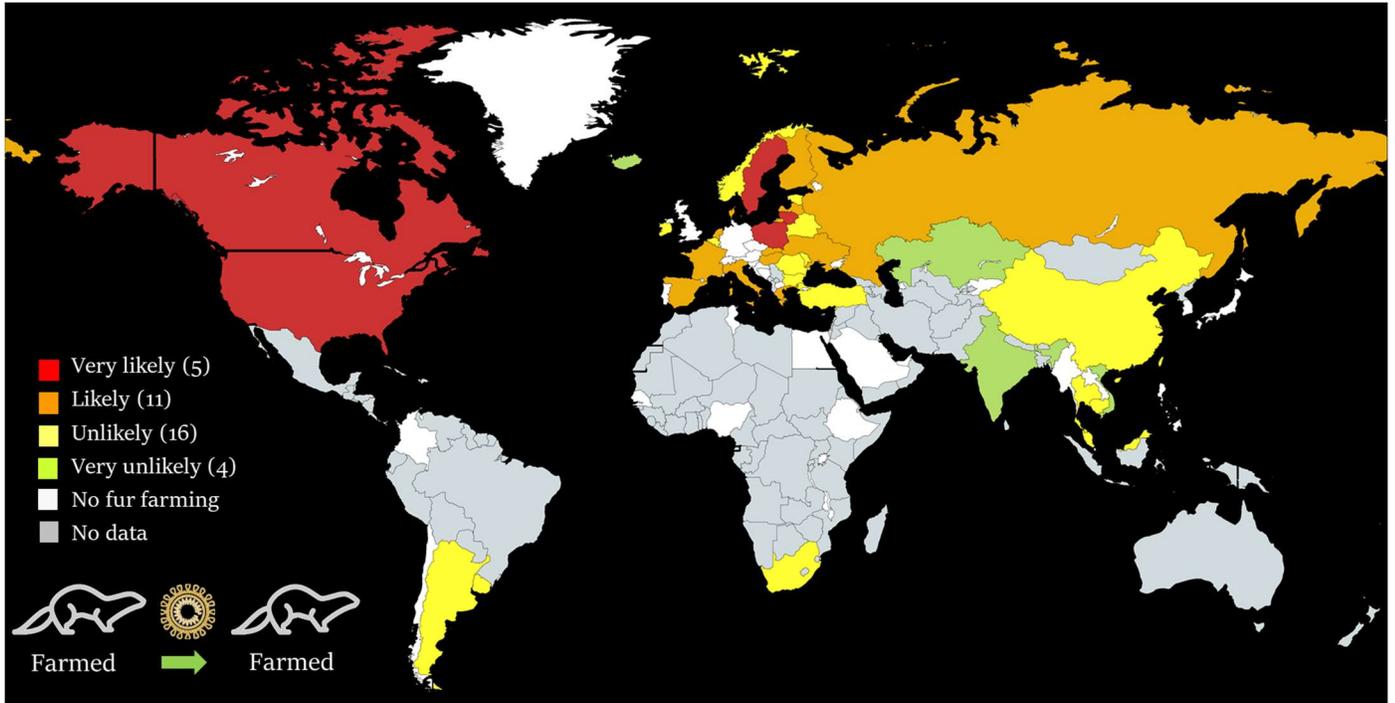
SARS-CoV-2 risk event	Graphic	U.S. risk
Introduction and spread within mink fur farms		<b>Very likely</b>
Spillover from mink farms to humans		<b>Very likely</b>
Transmission from fur farmed mink to susceptible wildlife		<b>Likely</b>



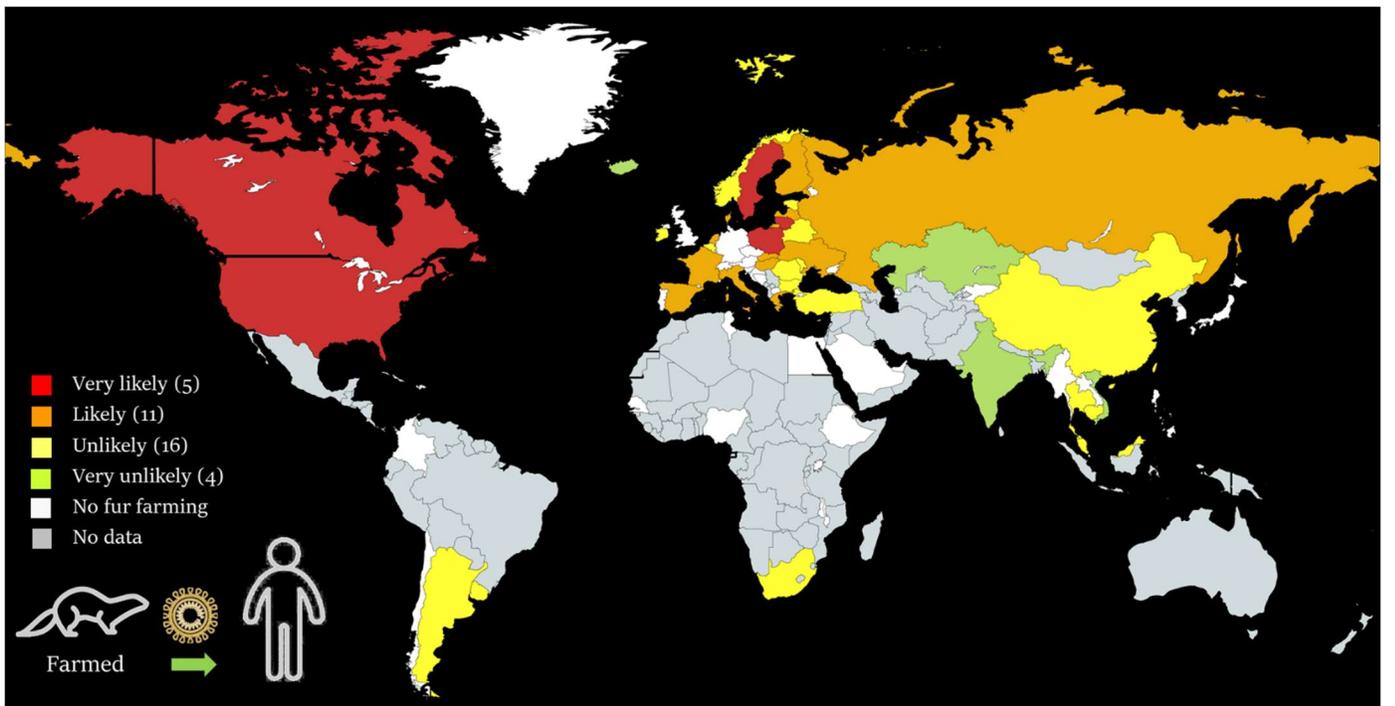
The likelihood maps of the three adverse SARS-CoV-2 outcomes from mink farming in all 36 countries examined are shown in **Figures 9A, 9B, and 9C**. *The U.S and Canada had the highest risks of any nation.* The 36 nations that host fur farms (primarily but not exclusively mink) are:

Argentina, Belarus, Belgium, Bulgaria, Cambodia, Canada, China (People’s Rep. of), Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, India, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Malaysia, Netherlands, Norway, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Thailand, Turkey, Ukraine, United States of America, Uruguay and Vietnam.

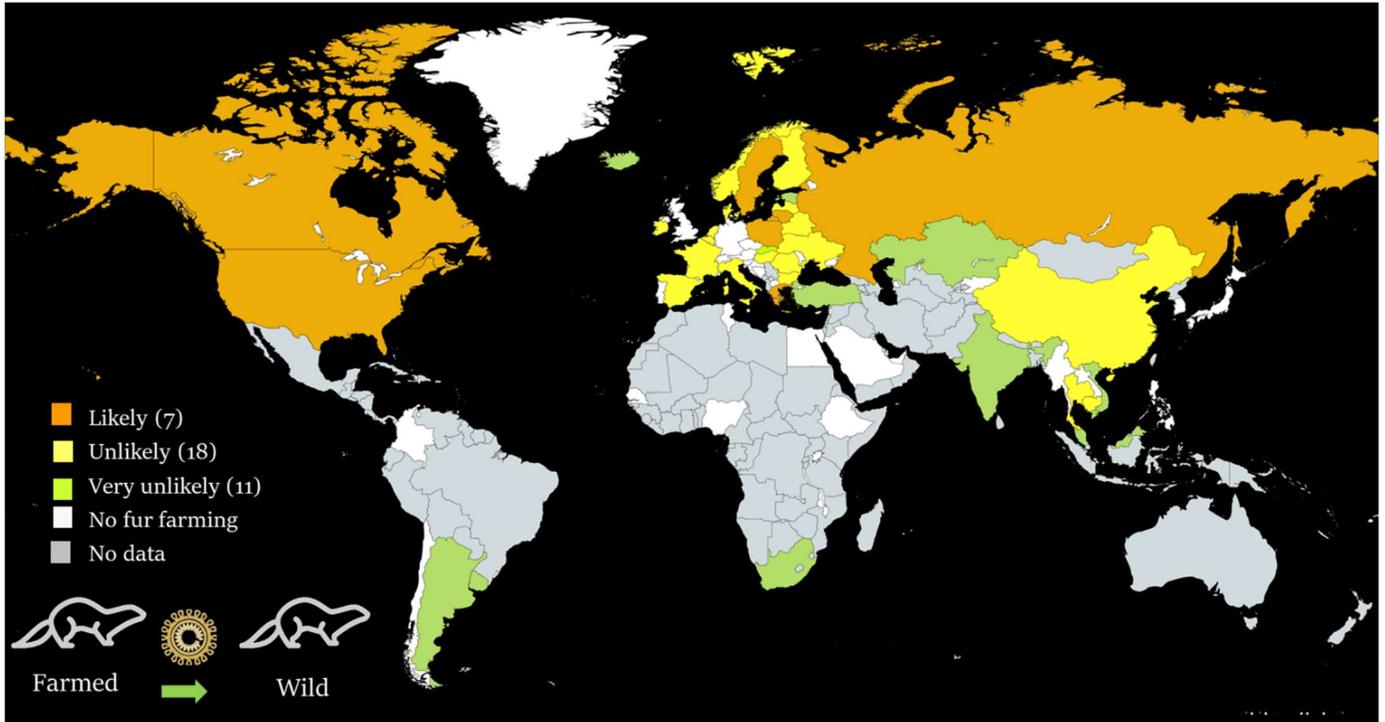
**Figure 9A - Likelihood of SARS-CoV-2 introduction and spread within mink farms in 36 fur farming nations as of 1.20.2021.** Risk defined as a function of five factors: (i) farmed mink density; (ii) biosecurity level in fur farms; (iii) confirmed cases in mink farms; (iv) human COVID-19 cases detected among workers on mink farms and communities near infected farms; (v) number of COVID-19 human cases in relative to human population per million (Modified Map 1, WHO/FAO/OIE 2021).



**Figure 9B - Likelihood of SARS-CoV-2 spill-over from mink fur farming to humans in 36 fur-farming nations as of 1.20.2021** (Modified Map 2 in WHO/FAO/OIE 2021).



**Figure 9C - Likelihood of SARS-CoV-2 spread from mink fur farming to susceptible wildlife populations in 36 fur-farming nations as of 1.20.2021.** Risk is defined as a function of four factors: (i) mink farm density; (ii) biosecurity level on fur farms, (iii) confirmed cases of SARS-CoV-2 in minks on fur farms; and (iv) presence of wild mustelids and canids in the country (Modified Map 3 in WHO/FAO/OIE 2021).



### **9. A history lesson, a cautionary tale, and call to action against SARS-CoV-2 in farmed mink ...**

*Chronic Wasting Disease* (CWD), a uniformly fatal slow-onset neuro-degenerative disease of Cervidae (the deer family), is a dramatic reminder of the huge potential downside of unnatural and exploitative farming of wildlife. CWD or “Zombie Deer Disease” is a transmissible spongiform encephalopathy (TSE) like Mad Cow Disease in cattle, scrapie in sheep, and Creutzfeldt-Jakob Disease in people. TSEs are caused by an abnormal infectious and transmissible protein called a “prion” that creates vacuoles (holes) in neurons that slowly destroy the brain and spinal cord with lesions similar to Alzheimer’s disease. (Ranched mink also have a TSE: *Transmissible Mink Encephalopathy* (TME). Outbreaks of TME are linked to feeding slaughterhouse offal from non-ambulatory (“downer”) or dead cattle and sheep. Ranched mink are no longer fed central nervous tissue from downer or dead ruminants and TME outbreaks are now rare. Thus TME likely represents prion “species jumping” of Mad Cow Disease or scrapie from ruminants into mink.)

CWD emerged in 1968 in a captive government mule deer herd in Colorado. It marched steadily through commercial deer and elk farms and spilled over into wild cervids by 1981 (Carlson et al 2018). CWD’s origin and dissemination trace directly back to past practices of the captive cervid industry including self-regulation, lax bio-security, little veterinary oversight, escaped farmed deer, fence-line contact with wild cervids, poor record-keeping, high-density confinement, inbreeding, and

frequent animal translocations and sales (Pacelle 2020). Not surprisingly, the distributions of farmed cervid CWD outbreaks and wild cervid CWD occurrence overlap (**Figure 10A**).

Fifty years post-emergence, potentially zoonotic CWD continues to expand across North America through new and recurring outbreaks. CWD now infects and kills thousands of free-ranging deer, elk, and even moose in 25 states at enormous socio-economic and ecologic costs. The causative CWD prion is indestructible in the ambient environment. It inter-generationally infects wild and captive cervids since it is transmitted by simply eating the grass growing in forever-contaminated soil. Thus CWD will never be eradicated. In parts of Wyoming, Colorado, Wisconsin, and Iowa, CWD prevalence in free-ranging cervids exceeds 40%, destroying local hunting economies, threatening the health and viability of white-tailed deer, mule deer, and elk populations, and putting humans who consume venison or closely contact deer at potential zoonotic risk.

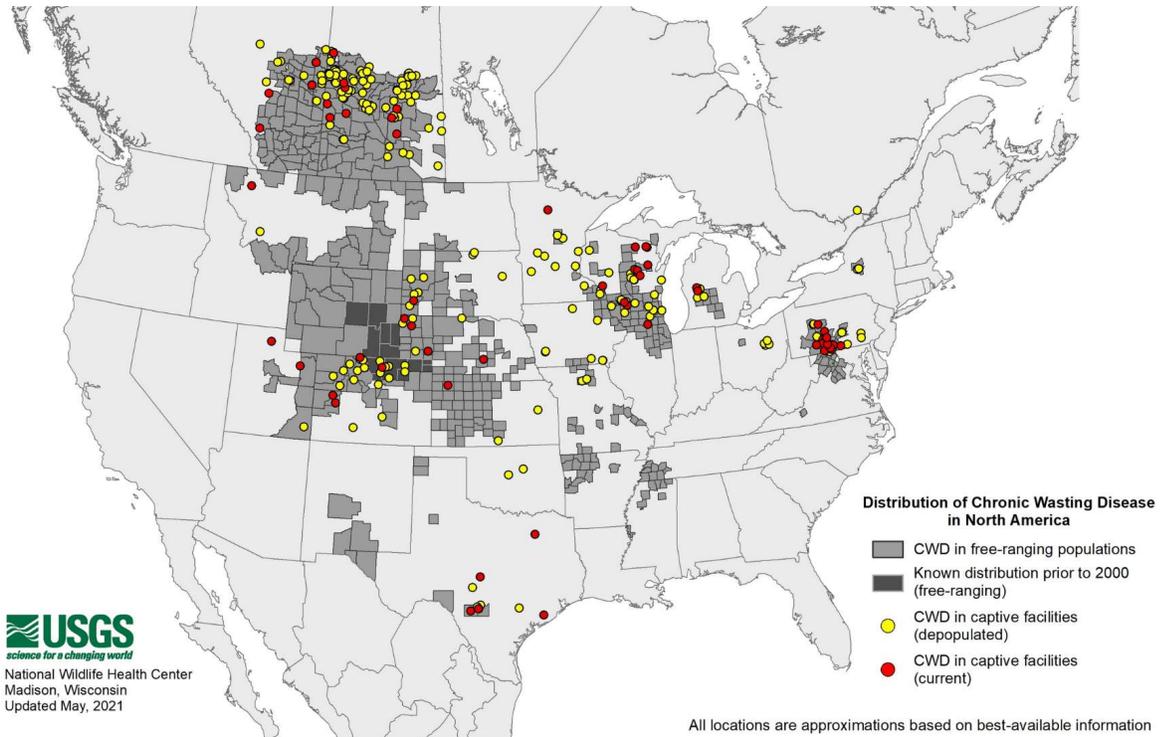
“History never repeats itself but it rhymes,” said Mark Twain. Many of the same cervid game farm risk factors that spawned and propagated the CWD epidemic exist now on mink ranches for SARS-CoV-2 including:

- Modest biosecurity (pre-COVID-19; likely improved post-COVID-19)
- Lax or self-regulation
- Industry secrecy
- Escaped animals
- High density-low welfare confinement
- Poor sanitation - unavoidable given high animal densities
- Inbreeding for genetic improvement (but lowers disease resilience)
- Highly stressed animals.

A bad or unnatural environment selects for injurious outcomes as predictably as antibiotic abuse selects for bacterial resistance. High consequence pathogen outbreaks in farmed wildlife that spill-back to people or spill-over to conspecific wildlife reservoirs are a very bad outcome indeed (**Figure 10B**).

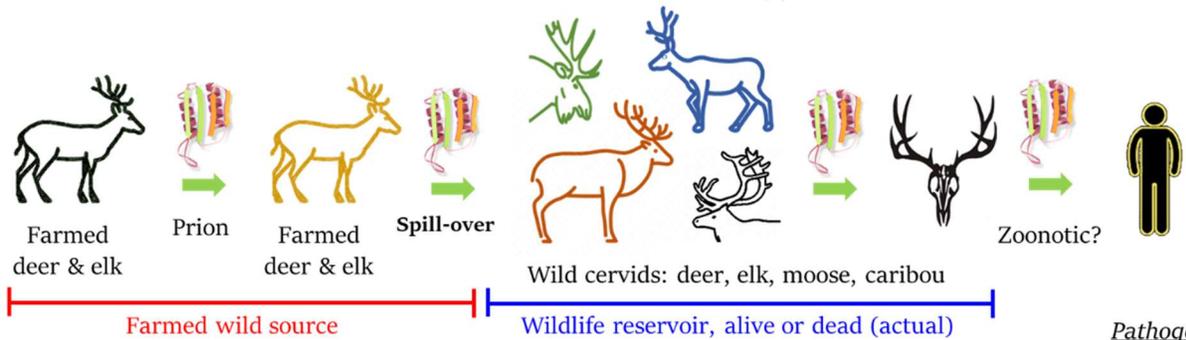
We were caught unawares by CWD and we must now contend with the consequences indefinitely. It is not yet too late to address SARS-CoV-2 in farmed mink. *We can prevent a high consequence anthropogenic SARS-CoV-2 disaster and tragedy in the future by aggressive, timely, and coordinated efforts in the present.* We can thwart zoonotic SARS-CoV-2 human spillback, virus mutant escape from vaccines and treatments, and permanent spillover from ranched mink into wild mink or other free-ranging animal reservoirs. The critical first step, in societal self-interest, is to *suspend and then ban high-risk mink farming as quickly as possible.*

**Figure 10A - North American distribution of Chronic Wasting Disease in wild and captive cervids.** Note the strong geo-correlation between infected captive game farms and infected free-ranging deer and elk counties.



**Figure 10B - Farmed wildlife: high consequence pathogen spill-over and spill-back**

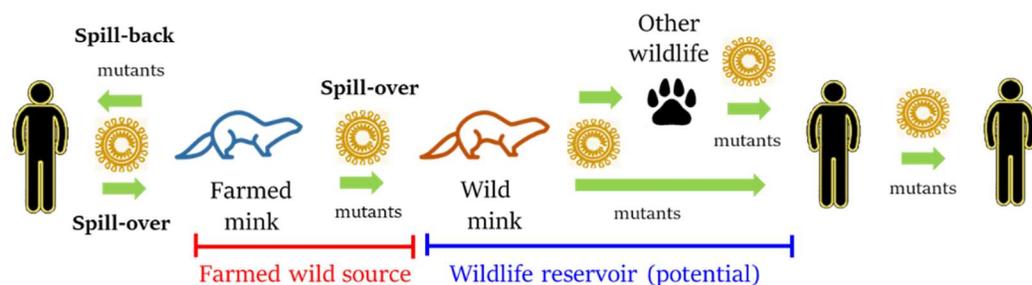
**A - Chronic Wasting Disease (CWD) in game-farmed & free-ranging wild cervids**



*Pathogen key*



**B - Zoonotic SARS-CoV-2 in farmed mink & free-ranging wild mink**



## ***Supplement 2 - Background information on wild and farmed mink and relation to COVID-19 risk***

**1. The wild American mink** is a small but aggressive semi-aquatic strict carnivore and predator in the Mustelid (weasel) family. The only other extant mink species is the critically endangered and smaller European or Russian mink, *Mustela lutreola* which is not used for captive mink farming. The American mink is native to Canada and the United States including Alaska but excluding the desert southwest (**Figure 2**).

Wild mink always live near streams, rivers, lakes, swamps, and marshes preferably with heavy vegetative cover. Mink are amphibious with a strong instinct and desire to swim and dive. Their outer fur coat of long oily guard hairs repels water while their dense fur undercoat is not waterproof but provides winter warmth.

Most mink activity is crepuscular and nocturnal. Except for the brief spring breeding season, mink are solitary, even anti-social. Males defend their territories from other mink, sometimes to the death. Each one marks its area with a typical scent. Water's edge territories vary in size from a few acres to hundreds of acres depending on resource richness.

Mink are ecologically important generalist and opportunistic predators of waterside animals such as muskrats, fish, frogs, shrews, rabbits, and mice. Their nocturnal, secretive, and roaming nature make precise mink population sizes difficult to ascertain but they are common in the U.S. (<https://www.cabi.org/isc/datasheet/74428#toDistributionMaps>). While the number of mink in an area depends on the amount and quality of available habitat, there is usually about one mink for every 50 acres of wetland habitat and three or four mink for each mile of good stream habitat (FCUSA 2021). These two brief videos demonstrate their solitary, active, and semi-aquatic natures: [https://youtu.be/po\\_vrwPp\\_TI](https://youtu.be/po_vrwPp_TI); <https://youtu.be/InZoFfSIbgE>.

The mating season runs from January through April. Both sexes are promiscuous. Females birth litters of three to six young in a fur-lined nest after a 42 day gestation period modified by delayed embryo implantation and rear kits alone. Kits are weaned when they are about six weeks old but stay with their mother until the fall. On average, wild mink live for 3-4 years but if they survive kit-hood they can live for a decade. Female mink are sexually mature by 1 year of age. Male mink reach maturity at about 18 months and are 25% (or more) larger than females. Wild mink are legally trapped for their fur in 47 states. Predation (especially of kits) by coyotes, snakes, birds of prey, disease, road accidents, and legal trapping constitute the primary set of mortality factors.

**2. The farmed American mink** - To provide a more reliable source of their luxurious winter pelts than a declining wild harvest could provide, mink have been fur farmed in the U.S. since the late 1800s. Mink farming, also called “ranching”, then spread to much of northern Europe and Asia starting in the early 20th century. Europe (Western and Central), Russia, and China now produce about 90% of farmed mink pelts. In 2019, the 2.7 million pelts produced in the U.S. represented just 5% of the 60 million mink pelts produced globally.



**Wild European mink**



**Wild American mink**



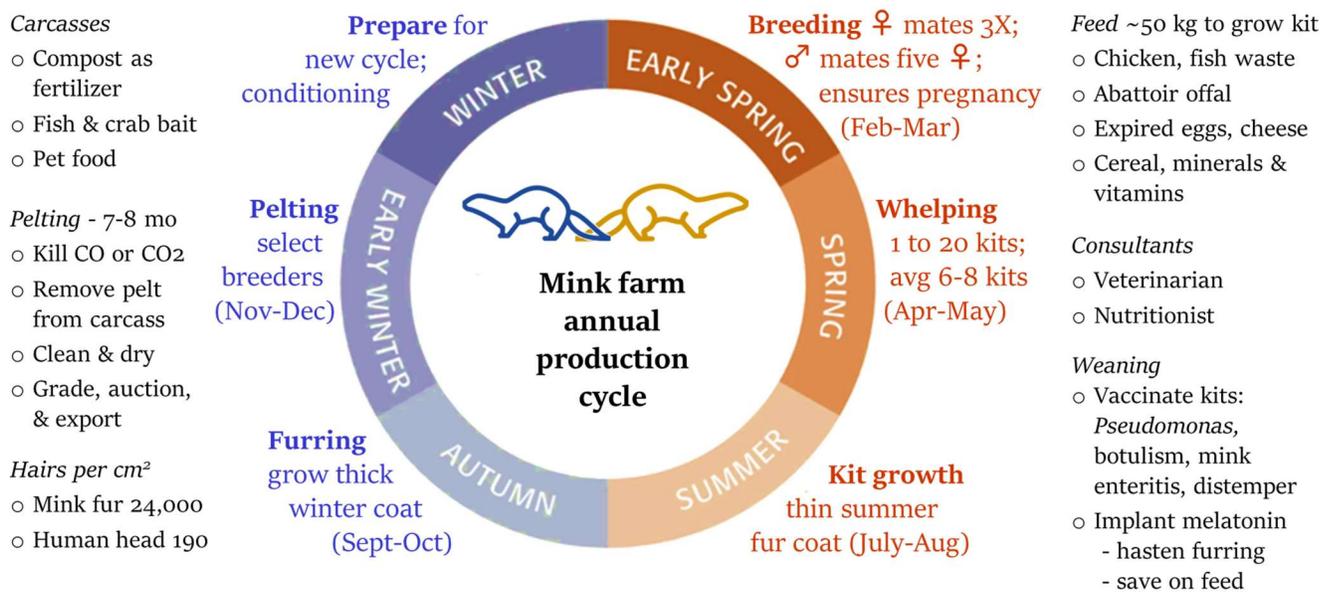
**Escaped feral American mink**

**Box 5 - The two species of wild mink.** The critically endangered European (or Russian) mink (*Mustella lutreola*) has a rapidly dropping remnant wild population of 30,000 animals in enclaves in France, Spain and Russia. Disease spread by and competition from non-native introduced or farm-escaped American mink (*Neovison vison*) are drivers of its decline.

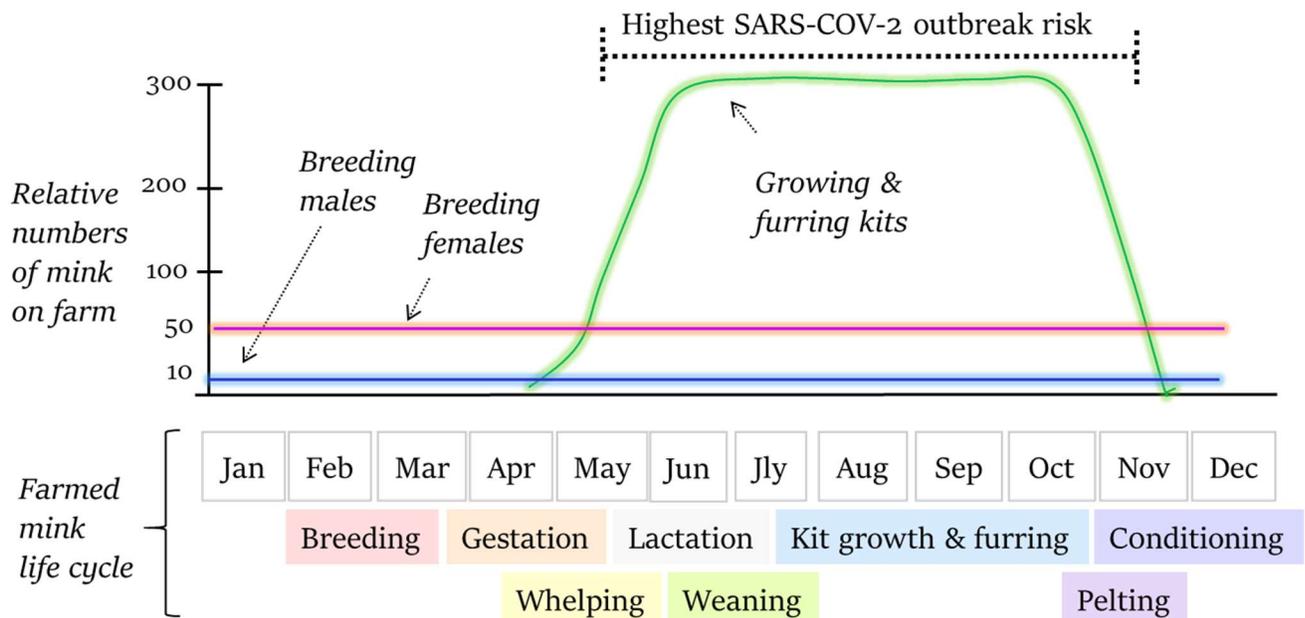
In North America, SARS-CoV-2 spread from farmed mink could harm both native wild American mink and endangered mustelids such as the black-footed ferret. The non-brown coat color and larger body size identify mink as feral or escaped.

**Figure 11** illustrates a typical annual production cycle on a U.S. mink farm. Females bred in late winter give birth in early spring to six or seven kits. The kits are weaned when six to eight weeks old and are grown out to winter furring to be pelted (killed for fur) at about seven months of age in November (NAFIC 2021). **Figure 12** shows relative mink farm population changes over an annual production cycle.

**Figure 11 - Yearly production life cycle of farmed mink**



**Figure 12 - Relative changes in mink farm census over an annual production cycle.** There are two separate “herds” on a mink farm: (1) the large furring herd of immature mink of both sexes that are born in spring and pelted in late fall, and (2) the smaller breeding herds of adult male and female mink. Female breeders usually outnumber males at about a 6:1 ratio, as in most agricultural animal settings.



**Phenotype** - Due to intense genetic selection and management practices targeting larger body size (and thus pelt size), larger litters, diverse pelt colors, and other human-desired traits over the past 150 years, farmed mink may differ greatly in outward appearance (phenotype) from their wild mink relatives. For example, an adult male farmed mink is loose skinned and weighs ~8 lbs. while a wild adult male mink is svelte and weighs ~3 lbs. There are more than 26 farmed mink coat color phases from white to black to pied; wild mink coat colors occur only in shades of dark brown. As in wild mink, farmed females are smaller than males.

**Environment** - The mink ranch contrasts sharply with natural wild mink habitats. Farmed mink are usually reared under industrial factory-like conditions including metal wire cages, concrete floors, piped drinking water, mechanized food delivery, highly processed semi-liquid diets, and heavy equipment and machines. Indoor housing in large barns or metal buildings on farms with 10,000 to 50,000 mink is the norm. Mink are also reared in large rows of outdoor sheds.

For their entire seven-to-eight month lifespan from spring birth until fall pelting (euthanasia and removal of winter pelt), the non-breeder furring mink are confined to small (12” H x 15” W x 24” L for two mink) metal or wooden cages (usually in pairs) and closely packed with hundreds to thousands of other caged mink. They are denied access to water for swimming and diving, a deprivation of a strong evolutionary instinct that provokes a measurable hormonal distress response (Mason et al 2001; Vinke et al 2008).

Schaffner (2021) noted: “Unlike domesticated farmed animals who have been in captivity for over 5,000 years, mink have been held in captivity a mere 90 years, and thus retain many of their wild instincts. Mink are “highly active and inquisitive animals,” instinctively nomadic with home ranges

in the U.S. of three to six miles. Nevertheless, the average cage in which a mink spends its entire life is one foot high, one foot wide, and three feet deep. Also, as semi-aquatic animals, they are physiologically hardwired to seek large bodies of water for diving, hygiene, and food. The intensive confinement and lack of bodies of water and other accommodations to satisfy their needs lead to physical and emotional suffering.”

Mink are fed an unnatural (if nutritionally complete) diet consisting of a *wet cat food-like mélange* of meat, poultry and fish industry waste, food animal by-products and slaughterhouse offal supplemented by expired human food (e.g. bread, milk, and cheese), and vitamin and mineral supplements. Mink are usually implanted subcutaneously with the hormone melatonin to hasten winter furring and thereby save feed costs, the greatest mink farm expense. The timing of early life cycle bio-driven events (breeding, whelping, lactation, and weaning) are similar between farmed and wild mink (**Figure 11**).

*Summary* - The management and housing of farmed mink deprive them of the four elements that most define the life of free-ranging wild mink: *hunting, solitude, swimming, and roaming*. The farmed mink tradeoff is a short, tedious and stressful life with plentiful (if unappealing) food. However, the evolutionary brief 150 years of mink domestication did not change the essence (“telos” i.e. intrinsic nature) of being a mink (Rollin 2016).

**A - Susceptibility to SARS-CoV-2 and other infectious diseases** - Mink have an innate predisposition to infectious diseases. This feature combined with the vast differences in wild versus farmed mink in phenotype, lifestyle, diet, genetics, animal density, housing, and baseline distress levels goes a long way in explaining the exquisite susceptibility of farmed mink to infectious diseases in general and to infection, disease, death and spill-back from the novel zoonotic SARS-CoV-2.

There are *unintended if predictable disease consequences* to raising mink under stressful environmental conditions to which they are evolutionary maladapted. The same high-volume-low welfare intensive confinement conditions that simplify mass-rearing of mink also create ideal conditions for pathogens like SARS-CoV-2 to prosper and evolve.

- Farmed mink are infamous for their vulnerability to disease epidemics e.g. distemper virus, influenza, and especially Aleutian disease and SARS-CoV-2. This innate weakness requires extreme bio-security precautions to prevent outbreaks.
- Unlike most animals, farmed mink (and some other Mustelids e.g. ferrets) are susceptible to spill-over (species jumping) virus infections from several different vertebrates including birds (Newcastle disease, avian influenza H5:N1); dogs (canine distemper), pork (pseudorabies herpes virus), and humans (influenza, SARS-CoV-2) (Fenollar 2021).
- Mink are solitary anti-social animals that *instinctively social distance* between their large defended territories. Their immune system evolved to deal with infrequent, low-dose pathogen encounters in the open air and rare or short-term seasonal contact with other mink. Thus mink farms are an extreme immune system challenge to even the most resilient of mink.
- Mink farms crowd thousands of animals indoors near hostile conspecifics, in intimate contact with their own and others bodily wastes and expired air. These are ideal conditions for SARS-CoV-2 that is transmitted by close contact, respiratory aerosols, and the fecal-oral route.

- The presence of viral lipid envelopes renders coronaviruses (including SARS-CoV-2) sensitive to environmental conditions such as desiccation, heat, extreme pH, UV light, and the presence of detergents. Prolonged exposure to unfavorable natural environments leads to rapid viral decay and loss of infectivity. The absence in mink buildings of disinfecting sunlight [whose UV wavelengths kill SARS-CoV-2 almost instantaneously (Tang et al 2021)] combined with large quantities of animal wastes [in which the virus can remain infectious for days (Guo et al 2021; Mohapatra et al 2021;)] are highly conducive to coronavirus environmental persistence.
- Innate susceptibility of mink to infections is worsened by physiological and behavioral distress. *Stress reduces immunity and contributes to minks' vulnerability to SARS-CoV-2 infection, disease, and death and ultimately to human risk.* Sources of (dis)stress in farmed mink include:
  - The mere nearby presence of other hostile mink e.g. released male mink often immediately fight each other. Mink possess an extremely well-developed sense of smell and scent mark their home territories. Confusing scent signals in a crowded barn may be overwhelming to mink, especially males. Unlike other agricultural animals e.g. cattle and swine, mink are not herd animals.
  - Tight confinement to small austere cages with minimal stimulation compared to a wild habitat.
  - Frustration at an inability to express instinctual behaviors especially swimming and diving. Mink have partially webbed feet. Wild mink spend about half their life in water (Mason et al 2001).
  - Semi-carnivorous scavenger farmed mink diet replaces a natural strict carnivore-predator diet.
  - Biological life-cycle stresses from the increased energy and metabolic demands of breeding, whelping, lactation, and weaning superimpose on ever-present stresses from mink farm management practices.
  - Inbreeding immune-suppression: For example, in describing SARS-CoV-2 outbreaks on Wisconsin mink ranches in 2020, *Golden (2021)* noted: “Captive mink have a flu season in the fall, just like people - they get it from us, in fact. But what appeared in the two mink farms in Taylor, Wisconsin, that saw outbreaks in October (2020) was not flu, which tends to sicken the weakest animals. This took out the strongest mink, the mature adult females. Over a few days, it killed hundreds per day and about 5,500 total on the two ranches. It whipped through by coat color, light to dark: The lighter-coat mink, ranch-bred to bring out recessive genes, have long been more delicate.”
- Mink farm population dynamics magnify SARS-CoV-2 risk. Farms undergo drastic population fluctuations each year during their annual production cycle (**Figure 12**). Animal census on mink farms is multiplied manifold (six times) in May when thousands of SARS-CoV-2 susceptible kits are born. Conversely, the farm mink population drops precipitously in late fall after pelting, consisting then only of adult breeding females, young replacement females, and male studs. Therefore, most mink farm SARS-CoV-2 outbreaks are expected to and do occur seasonally in summer and fall when numbers of susceptible mink are greatest.

**B - SARS-CoV-2 as a mink “Disease of Production”** - In veterinary medicine, the term “*disease of production*” (DOP) refers to an intensive animal management-linked infectious, metabolic, or other

disease or disorder (Nir Markusfeld 2003). A DOP either occurs exclusively in high input-high output-high confinement (“factory farmed”) animal production systems, or its prevalence and severity are higher compared to more extensive animal-rearing settings. DOPs are somewhat analogous to human occupational diseases as the DOPs are specific to certain types of livestock systems. For example, mastitis, infertility, and lameness are three important DOP in large high-performance dry lot dairy herds. Generally, the higher the herd production level, the greater the prevalence of any given DOP. Thus, *production diseases* may be considered a man-made problem.

High-producing agricultural animals (farmed mink inclusive), are challenged by many disease risks such as a taxing inbred genetic background, improper nutrition (deficit, surplus, or contaminant), poor sanitation, movement restrictive housing, high stocking density, harsh breeding practices, novel infections and stress (Nir Markusfeld 2003). Thus DOPs are multi-causal and inextricably linked to the inherent conflict between animal well-being and the economics of maximized animal production.

- A common view among people who raise agricultural animals and even some veterinarians is that “If livestock or poultry are producing and reproducing then their health and welfare is fine,” (Gunnarsson 2006). The SARS-CoV-2 outbreak that resulted in the deaths of 20 million farmed mink in 2020 challenges this assumption.
- We argue that SARS-CoV-2 in farmed mink is largely a DOP. A root cause is the huge discrepancy between how farmed mink are raised and the polar opposite world that wild mink inhabit.

**C - The critical role of human contact** - There may be wild animal species that are highly susceptible to spillover infection as a SARS-CoV-2 recipient host but we will never know because the animals never have contact with infected people or the virus.

The history of the first SARS-1 epidemic (2002-2004) and its anthropogenic underpinnings is revealing. The first SARS outbreak originated in China in 2002. SARS-1 infected 8,422 people and killed 916 people in 29 countries, a mortality rate of 11%. The palm civet cat (*Paguma species*), which was raised for food and sold in wet markets, was eventually identified as the SARS-1 intermediate host connecting bats and people (Guan et al 2003). No cases of SARS-CoV-1 have been reported worldwide since 2004.

In wet markets, food animals are sold either alive or as fresh meat. Due to the culinary preferences of the southern Chinese, their wet markets were filled with a large variety of wild animals. The presence of many different animal species in cages near one another in wet markets and the fact that these markets were located near residential areas in most parts of China allowed frequent contact between humans and these animals that might be carrying new viral diseases. This provides an ideal scenario for the emergence of novel viruses that can jump species barriers.

In 2003, China banned holding wildlife at wet markets after the 2002–2004 SARS outbreak. But the restrictions on selling live wildlife were fleeting, and the government of China promoted an expansion of wildlife selling at live markets in the succeeding years for rural development and poverty alleviation. The wildlife-farming industry was valued at 520 billion yuan (\$74 billion) in 2017 (Beech 2020).

*Wong et al 2019*: “A common phenomenon observed in both SARS-CoV [in 2003] and SADS-CoV [swine acute diarrhea syndrome coronavirus, a bat-borne coronavirus that killed 24,000 pigs in China in 2017] outbreaks is that the outbreaks involved caged or farmed animals that were restricted

to defined areas with bats inhabiting the areas around. In the case of SARS-CoV, civets in the wild were found to be free from the infection. In other words, human activities facilitated the viral spillover events by bringing susceptible recipient hosts to the vicinity of viral sources. Surveillance on interspecies transmission should be placed around wet markets, farms, and abattoirs to safeguard humans from novel zoonotic diseases.”

*Ying 2020*: “Before the SARS outbreak, there were nearly 1,000 civet farms in China. The biggest sales market of civet cats was in Guangdong Province. After masked palm civets were considered as possible SARS carriers, about 10,000 civet cats were culled in January 2004. The price of one kilo of civet meat slumped from over 200 yuan to less than 40 yuan, and still, people were unwilling to buy them, which was a big blow to the industry.”

*Woo et al 2006*: “In Chinese wet-markets, unique epicenters for transmission of potential viral pathogens, new genes may be acquired or existing genes modified through various mechanisms such as genetic reassortment, recombination, and mutation. The wet markets, at closer proximity to humans, with high viral burden or strains of higher transmission efficiency, facilitate the transmission of the viruses to humans.”

In early 2020, the Chinese government shut down thousands of wet markets after finding an epi-link between the SARS-CoV-2 outbreak and a Wuhan wet market. *Standaert (2020)* wrote: “Nearly 20,000 wildlife farms raising species including peacocks, civet cats, porcupines, ostriches, wild geese, and boar have been shut down across China in the wake of the coronavirus, in a move that has exposed the unknown size of the industry. Until a few weeks ago wildlife farming was still being promoted by government agencies as an easy way for rural Chinese people to get rich.”

One is reminded of George Santayana’s 1905 observation, “Those who cannot remember the past are condemned to repeat it.” *There are obvious if uncomfortable SARS-2 and SARS-1 disease risk correlates* between how we raise farmed mink for fur in the U.S. and how the Chinese raise wildlife to supply wet markets in at least three ways:

- (1) The *opportunity* for daily close contact between people and farmed (wild) animals.
- (2) The *conflict* between the public policy need to support the economic livelihoods of rural people who raise animals and prudent veterinary public health practice.
- (3) The *inevitability* that intensive animal agriculture, whether mink (SARS-CoV-2) or poultry (Influenza H5:11) or civet cats (SARS-1), often carries with it real-world zoonotic disease risk consequences. The two cannot be disentangled.

**3. Comparison of farmed and wild mink** - A summary of major differences between farmed and wild mink that drive mink SARS-CoV-2 spillover, spill-back, and species jumping is shown in the pictogram in **Figure 13**. Photographs that compare appearance, habitats and living space, diet, and daily life of farmed versus wild American mink are shown in **Figures 14A, B, C, and E**. Visible and invisible consequences of high stress on farmed mink are described in **Figure 14D**.

**Masked palm civet (*Paguma larvata*)**



**Figure 13 - Denatured conditions drive infection and transmission risk in farmed mink**

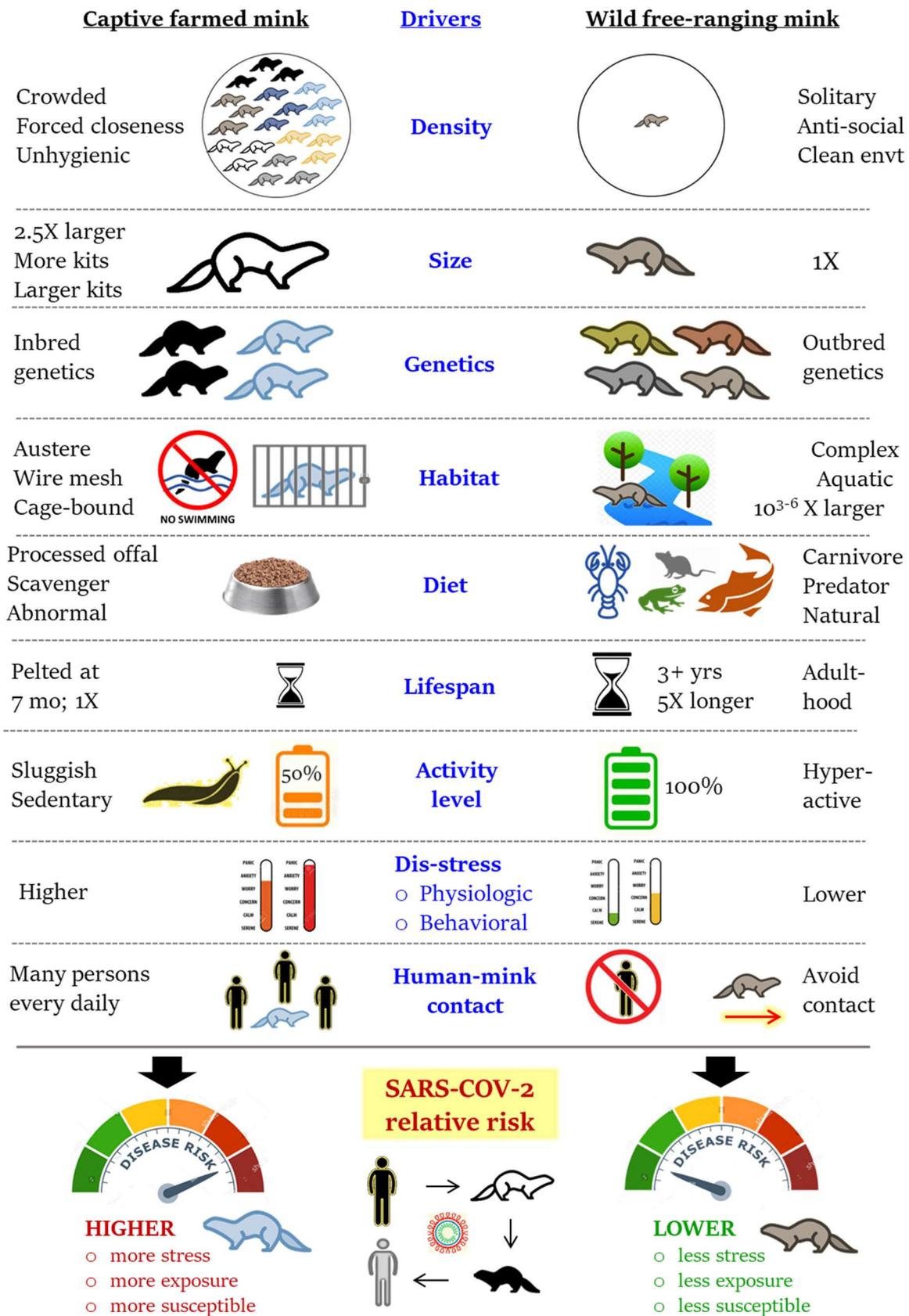


Figure 14A1 - Phenotype comparison of wild free-living vs. farmed American mink



Trait	Wild	Farmed
Head	Wedge shaped, sharp features Note embedded porcupine quills	Large with rounded features
Eyes & ears	Proportionately larger	Proportionately smaller
Nose	Smaller	Larger
Fur	Long oily guard hairs (water-proofing); normal undercoat	Short guard hairs; dense velvety under-coat
Coat color	Solid brown	More than 24 color phases both solid and pied
Adult weight	3 lb (male)	8 lb (male)
Body shape	Slight build; designed for speed & athleticism	Bulky build; bred for excess skin; often heavy set



Figure 14A2 - Comparison of wild free-living vs. farmed mink habitats and living space



High density Wisconsin industrial mink farm



Natural riverine mink habitat in Oregon



The Fur Commission USA guidelines (2019) minimal cage size for two mink is 12”(H) x 15” (W) x 22” (L) = floor space of (15” x 22”)/2 = 165 sq in = 1.15 ft<sup>2</sup> per mink

*Lifestyle* - sedentary, claustrophobic, crowded



Crowded reality; never swim or dive entire life



Smallest wild mink territory is ~10 yards (waterside) x 250 yards = 22,500 ft<sup>2</sup> or **19,000-fold larger** vs. farmed mink cage space. Largest mink range of 2,500 acres = **94 million fold larger** vs. allotted cage area

*Lifestyle* - active, solitary, semi-aquatic



Solitary wild mink spend about 50% of their active periods swimming and diving

**Figure 14B - Diets of farmed mink vs. wild mink.** Feed is the largest cost incurred by fur farms at 50-60% of the total cost of producing a pelt. Farmed vs. wild mink diets are completely different.



*Farmed mink* - Semi-solid wet-cat food like mix of by-products and waste from human food production especially high-protein ingredients e.g. dairy, fish, cheese and meat, fish filleting waste, poultry processing and slaughterhouse offal

*Wild mink* - Carnivorous opportunistic predator of live fish, small mammals, birds, reptiles, amphibians, crustaceans, even prey as large or larger than they themselves are e.g. muskrats

**Figure 14C - Visible and invisible impacts of high stress on farmed mink.** Self-mutilation (e.g. tail-biting), cannibalism (e.g. head and neck wounds) and bar chewing are *visible manifestations* of high stress, under-stimulated, crowded, and impoverished farmed mink environments. *Immuno-suppression* is an *invisible manifestation* of high stress and unnatural mink farm environs and is a driver of SARS-CoV-2 and other infections on mink ranches.



Cannibalism



Biting pen-mate



Cannibalism



Cannibalism



Self-mutilation: tail-biting



Bar chewing



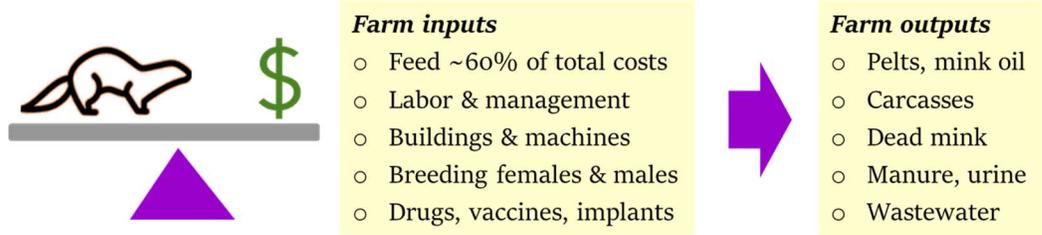
**Figure 14D - Denatured farmed mink.** The management and housing of farmed mink deprives them of the four elements that most define the life of free-ranging wild mink: **solitude, hunting, roaming and swimming.** The farmed mink tradeoff is a short, tedious and stressful life with plentiful (if unappealing) food. The evolutionary brief 100-150 years of mink domestication did not change the essence (“telos” i.e. intrinsic nature) of being a mink.



4. **The U.S. farmed mink industry** peaked in numbers of animals housed and economic impact in the 1950s-1970s when mink furs were in demand by high-net-worth individuals willing to pay handsomely for a fur coat. Mink ranch numbers peaked at 7,200 in the mid-1960s.

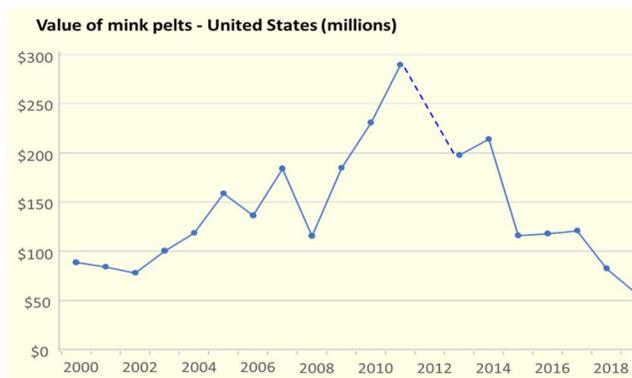
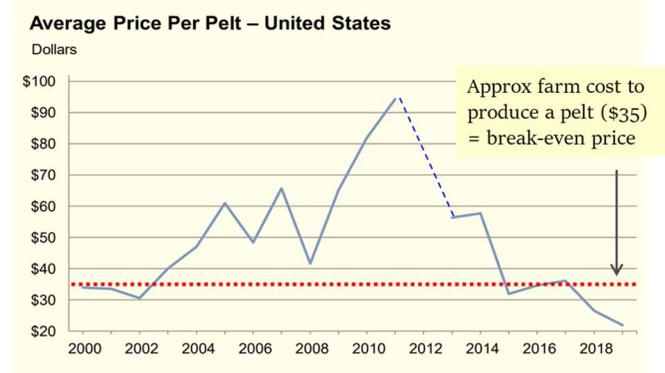
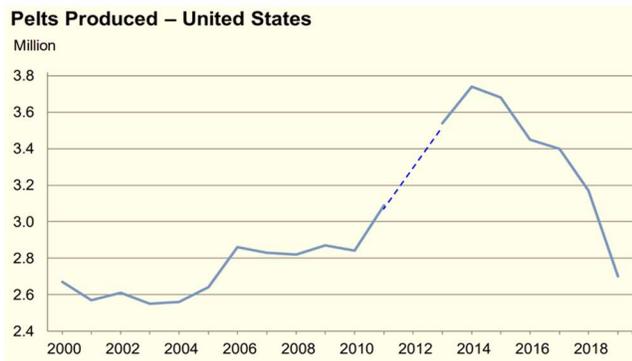
**Figure 15** is a simple microeconomic model of a U.S. mink farm showing major inputs and outputs. The biggest input is feed and the biggest output is fur pelts. Mink farmers also earn income from mink oil (from abdominal fat) and from composting pelted carcasses and animal wastes into garden or crop fertilizer. Pelted carcasses can be recycled as commercial fish or crab bait or used in pet food.

**Figure 15 -**  
Simple mink farm microeconomic model



**Figure 16** is a macro-economic view of U.S. mink farming over the past two decades. A slow increase in production and pelt prices from 2000 to 2014 was followed by a production and pelt price crash in the years since 2014. The price collapse was caused by over-production, especially in China. The U.S. price and production nadir occurred in 2019 with a record low average price per pelt of \$21.90, far below the average cost to produce a pelt (the break-even price) of ~\$35. The global pelt price increased by 40% in early 2020 due to the loss of the 20 million pelts from SARS-CoV-2 mink culling in Denmark and the Netherlands.

**Figure 16 - U.S. mink pelt production, the average price per pelt, and farm-gate value of mink industry** (Farm-gate value = No. of pelts produced x Average price per pelt).



**Decline of U.S. farmed mink industry ...**

- U.S. mink farm profits reached historic highs in 2011 due to rapidly increasing consumer demand in China and Russia.
- Since 2011, the U.S. mink pelt market rapidly deteriorated in both (1) no. of pelts produced and (2) average price per pelt. Total farm-gate value of mink pelts also plummeted.
- Pelts produced in 2020 declined to 20 million while pelt price increased to \$40, perhaps the first profitable year since 2014.
- World mink price rose by ~40% in early 2021 due to loss of ~20 million European mink pelts due to COVID-19.

USDA National Agricultural Statistics Service, July 2020; no data for 2012

In **Table 6** the percent change in average pelt price, number of pelts produced, and industry farm gate value are compared between 2020 and 2019 (*the most recent trend*), 2020 and 2019 (*worst year ever to farm mink*), and 2020 vs. 2011 (*best year ever to farm mink*). The mink industry responds quickly to market changes in pelt demand by keeping more or fewer female mink back as new breeders at fall pelting.

**Table 6 - U.S. mink farm macro-economic comparisons: 2011 vs. 2019 vs. 2020**

Year	Avg. cost to produce pelt	Avg. market price pelt <sup>a</sup>	No. pelts produced	Farm-gate value	Comments
<b>2011</b>	~\$35	\$94.30	3.1 M	\$292.5 M	Best year ever
<b>2019</b>	~\$35	\$21.90	2.7.M	\$59.2M	Worst year ever
<b>2020</b>	~\$35	\$40.00 <sup>b</sup>	2.0 M	\$80.0 M	Improved year
<b>% change 2020 vs. 2019</b>	NA	<b>+83%</b>	<b>-26%</b>	<b>+35%</b>	2020 better than 2019 ...
<b>% change 2020 vs. 2011</b>	NA	<b>-58%</b>	<b>-35%</b>	<b>-73%</b>	But 2020 is still far below 2011

Note: Break-even price (\$35) is *greater than* average pelt price in 2015, 2016, 2017, 2018 & 2019

<sup>a</sup> Global pelt price in 2021 is expected to increase by at least 40% due to the loss of 20 million pelts in Europe (1/3 of global supply) from SARS-CoV-2 mink deaths and culling

<sup>b</sup> Pelt price increase in 2020 due to lower global pelt production in response to historic low 2019 pelt price. No. of bred female mink to produce kits in 2020 =359,850 was down 48% vs. 2019 (USDA NASS)

Based on security concerns, the U.S. farmed mink industry husbands information about farm locations and other details. Neither the states nor Federal governments closely regulate the industry, so farm-level data is lacking in some cases. In 2019, 2.7 mink pelts were produced with a farm-gate value of \$59 million (USDA NASS 2020). The number of active mink farms is generally unavailable as these farms (at least pre-COVID-19) are not regulated by State or Federal departments of Agriculture.

- Wisconsin is the top producer (1/3 of U.S. pelts). Utah is second although it has the largest number of U.S. farms. Those two states and Idaho, Iowa, Michigan, Minnesota, and Oregon produce well more than 85 percent of all pelts (USDA NASS 2020). According to the Fur Commission USA (a national, non-profit association representing U.S. mink farmers funded by a 15-cent assessment per mink pelt) in 2020, 120 mink farms produced 2.0 million mink pelts valued at \$40 per pelt and \$80 million farm-gate value (NAFIC 2021). This estimate of 120 mink farms, however, is inconsistent with our state-based research and *may be inflated*. The USDA will release 2020 mink production estimates on July 22, 2021.

- Farms range in size from a few hundred animals to many thousands per farm with an average of 15,000 mink per farm. Larger farms are often foreign-owned (Golden 2021). The U.S. produced ~5% of the world's 60 million pre-COVID farmed mink pelts in 2019.
- The average cost of production to raise a mink over nine months from spring breeding, gestation, and birth to fall pelting is as low as \$35 (Golden 2021) while the average price paid for a mink pelt in 2019 was just \$21.90 (USDA NASS 2020). *Pelt prices were below the break-even point from 2015 through 2019.* However, pelt price varies greatly year by year and is based on market demand, fur quality, pelt size, color, texture, and density. For example, the pelt price at the September 2020 mink pelt auction of the American Mink Exchange varied from a high of \$46.00 to a low of \$8.10 (American Mink Exchange 2020).
- Most U.S. mink pelts are exported to China or South Korea as raw material for luxury women's clothing.
- In the U.S., SARS-CoV-2 infected mink farms are quarantined by the USDA and CDC. Some European nations also adopted that strategy, while others, notably Denmark and the Netherlands, resorted to the mass killing of mink to address public and animal health threats. Fur production (along with new fur sales) is banned in California, while 12 European nations have banned or are phasing out fur production.
- Unfortunately for global public health, the farmed mink industry in China is taking advantage of the surge in global mink pelt prices and rebuffing calls to cease operations. Despite high SARS-CoV-2 risk from farmed mink, China is believed to be rapidly expanding production on its 3,000 to 8,000 mink farms which can raise up to 15 million animals (Tian & Stanway 2020; Faure & Sciami 2021). With the demise of mink farming in Denmark, China is almost certainly now the top producer of mink pelts in the world. *Note:* As in the U.S., precise numbers of farms and pelts produced in China are obscure.
- *Schaffner (2021)* noted: "... Fur farming is a cheap means for local governments to try to address poverty in rural communities and rustbelt regions where industrial workers have lost their jobs. ... one Chinese breeder's earnings increased 30-50% after the announcement of the cull in Denmark. Although China had banned all wildlife trading in response to the pandemic, the *government classified mink, arctic fox, and raccoon as "special livestock" exempt from the ban.* In China, many large breeders claim to have rigorous vaccination and hygiene regimes, and the government has administered free COVID-19 tests for captive mink since the Denmark cull was announced."

*Note* - Since this *Supplement 2* is designed to provide background information on wild and farmed mink concerning COVID-19 risk, we assembled eight Web links in **Table 7** with short quality videos including footage of wild mink, feral mink, and industry produced mink farm videos. It is essentially impossible to gain access to commercial mink farms due to the mink industry's security concerns so mink industry (or undercover) footage are the only available video sources.

**Table 7 - Informative web-based videos of wild mink, feral mink, and mink farms**

Video weblink	Post date	Length	Description
<a href="https://youtu.be/po_vrwPp_TI">https://youtu.be/po_vrwPp_TI</a>	April 21, 2021	2:39	Wild mink swimming & hunting
<a href="https://youtu.be/InZoFfSIbgE">https://youtu.be/InZoFfSIbgE</a>	April 21, 2021	4:25	Wild mink night and day at a burrow
<a href="https://youtu.be/oYe9CNw1gNA">https://youtu.be/oYe9CNw1gNA</a>	Oct 19, 2018	3:08	Semi-tame feral mink in Poland
<a href="https://www.euronews.com/2021/05/21/greece-s-mink-farms-take-a-different-approach-to-survive-the-covid-19-pandemic">https://www.euronews.com/2021/05/21/greece-s-mink-farms-take-a-different-approach-to-survive-the-covid-19-pandemic</a>	May 21, 2021	8:00	EuroNews report on COVID-19 impact in Europe; detail on Greece mink farms
<a href="https://youtu.be/wbb9agOXGt8?list=PL4SjZ4Wvr8Zk4snvxz371rr-Xm4T22Wsm">https://youtu.be/wbb9agOXGt8?list=PL4SjZ4Wvr8Zk4snvxz371rr-Xm4T22Wsm</a>	Dec 3, 2012	10:28	Overview of mink production; pro-mink industry viewpoint; shows industrial nature of mink farming
<a href="https://youtu.be/m7HT1xZ2VHU">https://youtu.be/m7HT1xZ2VHU</a>	Dec 13, 2017	6:52	360 tour of mink farm; shows industrial nature of mink farming; pro-industry
<a href="https://youtu.be/WwPsStvktks">https://youtu.be/WwPsStvktks</a>	Dec 2, 2014	7:02	Fur Commission USA pro-industry video on Zimbal mink farm in WI, one of largest mink ranches in the U.S.
<a href="https://youtu.be/meFB3EJWj-o">https://youtu.be/meFB3EJWj-o</a>	Aug 22, 2018	4:13	Video from Polish mink farm documenting poor mink welfare including severe cannibalism

## ***Supplement 3 - Feral farmed mink as an invasive and injurious species***

**1. Definitions** - An *invasive species* is an organism that causes ecological or economic harm in a new environment where it is not native. SARS-CoV-2 qualifies as an invasive species, and farm-escaped or feral American mink are legally classified as invasive species in several European nations (<https://www.cabi.org/isc/datasheet/74428#toDistributionMaps>).

According to the U.S. Fish and Wildlife Service (USFWS), *injurious wildlife*, as defined by the Lacey Act, includes wild mammals, wild birds, reptiles, amphibians, fishes, mollusks, and crustaceans that are harmful to other wildlife or humans and human interests like agriculture and forestry. There are 785 species of animals listed as “injurious” under the Lacey Act as of December 2020.

### ***2. Escaped and feral American mink as invasive***

Wherever mink are farmed in large numbers, they may escape due to their speed, muscular and narrow build, agility, and intense desire to be in and around water. In particular, mink escape from farms when they are moved out of their cages e.g. during mating and pelting. Many thousands of farmed mink escape each year worldwide. In some cases, farmed mink are deliberately released. Mink escaping or released from farms supply the feral population in Eurasia or supplement native populations in North America that surround mink farms. While their free-living survival rate is not known, some escaped mink survive as self-sustaining populations.

In Europe, feral American mink that escaped from fur farms are thought to play a large part in the decline of the critically endangered European mink (*Mustela lutreola*), mostly because of competition for resources by the much larger farmed American mink. American mink are also spread disease to European mink e.g. Aleutian disease. In many countries (e.g. England, Ireland, Iceland, Germany, Spain), feral American mink are considered an invasive species and are actively eliminated. Feral American mink pose a particular risk to island biodiversity especially to ground-nesting birds and small mammals which in certain circumstances they may have the potential to extirpate (Roy et al 2009). In Canada, wild mink numbers have declined over the past several decades based on trapping records. It is believed that escaped feral American mink are a primary cause of this wild mink decline.

The impact of escaped or feral “domestic” mink in the U.S. on native wild mink or other species is poorly studied but likely to be detrimental to natural riverine ecosystems in general, to biodiversity specifically, and wild mink in particular. The advent of SARS-CoV-2 introduces an even more meaningful viral threat to native mink, compounding the menace posed by the competition and intra-specific aggression risks posed by the much larger farmed mink.

While both farmed and wild mink are the same species (*Neovison vison*), farmed mink can be injurious to native American wild mink in at least four ways:

- (i) ***Physical domination***: Adult farmed or escaped feral mink are about twice the size of wild mink and may physically dominate wild mink. Farmed adult male mink reach 8 lb. body weight versus 3 lb. bodyweight of adult male wild mink. This phenotypic advantage of escaped farmed mink may allow them to outcompete wild mink for resources (e.g. territory, food, mates). For example, male

mink are intolerant of other males and fight for access to females in the spring breeding season, and may kill other males. Wild mink displaced from their home territory usually starve.

- (ii) **Genetics:** Escaped farmed and feral mink are known to hybridize with wild mink. Farmed mink may introduce maladaptive genetics leading to fitness loss in wild mink populations. Farmed mink may also possess greater fertility (e.g. larger litters) than wild mink. Wild mink birth one to eight kits, with an average of four kits per litter. Farmed mink (who are selected for high fertility) birth one to 20 kits, with a litter size of seven to eight most common.
- (iii) **Mink-specific diseases:** Farmed mink may introduce diseases into wild mink populations. Aleutian Disease (AD) of mink is the most serious disease of farmed mink worldwide and there is no treatment or vaccine. AD is caused by a parvovirus and provokes spontaneous abortion and death in wild and farmed mink and ferrets. The disease can be spread from farmed mink to wild mink and may be causing a decline in North American wild mink populations (Nituch et al 2011).
- (iv) **Zoonotic SARS-CoV-2:** Disease spillover from farmed mink to wild mink is a major concern with SARS-CoV-2. It has already happened. A wild mink infected with SARS-CoV-2 was trapped near an infected mink farm in Utah (Gorman 2021). The wild mink had the same SARS-CoV-2 strain as that found in the nearby mink farm. In addition, serum samples from eleven Utah mink farm escapees tested positive for SARS-CoV-2 antibodies by virus neutralization (Shriner et al 2021).



**Box 6 - Escaped male captive-born (left), male wild-born (middle) & female wild-born (right) mink in Denmark.** These mink were trapped for invasive species control. Farmed mink breeding males and females increased their mean body weight by 70% for the past 10–15 years in Denmark. A similar size increase likely occurred in U.S. farmed mink to increase pelt yield.

Besides appearance, escaped mink are identified by fluorescent tetracycline in their canine teeth. Tetracycline is an antibiotic used in farmed mink that wild-born mink should never be exposed to (Pagh et al 2019). *Note stark size and coat color differences between escaped captive vs. wild-born mink.*

### **3. Supporting quotes from the scientific literature on the injurious nature of farmed mink**

*Beauclerc et al 2013:* “We assessed the cryptic invasion of escaped domestic American mink (*Neovison vison*) within their native range. Feral mink are a known alien invader in many parts of the world, but the invasion of their native range is not well understood. We genetically profiled 233 captive domestic mink from different farms in Ontario, Canada, and 299 free-ranging mink from Ontario, and used assignment tests to ascertain genetic ancestries of free-ranging animals. We found that 18% of free-ranging mink were either escaped domestic animals or hybrids, and a tree regression

showed that these domestic genotypes were most likely to occur south of latitude of 43.13°N, within the distribution of mink farms in Ontario. Thus, domestic mink appear not to have established populations in Ontario in locations without fur farms.”

*Nituch et al 2011*: “Antibodies to AD (Aleutian Disease) were detected in 29% of [wild] mink (60 of 208 mink sampled); however, seroprevalence was significantly higher in areas closer to mink farms than in areas farther from farms, at both large and small spatial scales. Our results indicate that mink farms act as sources of AD transmission to the wild. As such, it is likely that wild mink across North America may be experiencing increased exposure to AD, via disease transmission from mink farms, which may be affecting wild mink demographics across their range. In light of declining mink populations, high AD seroprevalence within some mink farms, and the large number of mink farms situated across North America, improved biosecurity measures on farms are warranted to prevent continued disease transmission at the interface between mink farms and wild mink populations.”

*Bowman et al 2007*: “The feralization of domesticated species can have negative effects on native biodiversity, especially on the fitness of closely-related wild species. Negative effects on fitness can occur through a number of mechanisms, including the spread of disease, competition, and hybridization, with or without introgression [of genetic material]. For example, farm-raised elk (*Cervus elaphus*) have likely spread chronic wasting disease to wild cervids. Farmed Atlantic salmon (*Salmo salar*) are more aggressive than wild salmon, and thus may be more successful than wild salmon in competitive encounters.”

*Bowman et al 2007*: “We believe it is plausible that mink populations in Canada have declined due to outbreeding depression following hybridization between ranches and wild mink and introgression of ranch alleles into wild mink populations. Outbreeding depression may have resulted from a loss of local adaptation, the occurrence of maladaptive domestic traits, the breakdown of co-adapted gene complexes, epistasis, or any combination of these ... An alternative, potentially important mechanism for escaped ranch mink to affect wild mink populations is by introducing disease into the wild mink population. There are a number of diseases that can infect mink in ranches, including Aleutian disease, an often fatal parvovirus.”

#### ***4. Summary - three ways farmed mink are an “injurious species” to human, animal, and ecosystem health***

- (i) To people - a source, vector, and reservoir of mutant and non-mutant SARS-CoV-2 and potentially other human zoonotic pathogens such as influenza H5:N1
- (ii) To wild mink - the dimorphic advantageous body size and higher fertility of farmed mink may allow escaped farmed mink to dominate and perhaps even locally extirpate wild mink populations. Hybridization of farmed mink may introduce abnormal maladaptive fitness traits (e.g. color, size, behavior, etc.) into native North American wild mink populations. Farmed mink also introduce new (e.g. SARS-CoV-2) and old diseases (e.g. Aleutian Disease, influenza) into wild mink populations. Finally, feral and escaped mink compete for food, mates, territory, and other resources with wild mink.
- (iii) To other wildlife - Farmed mink are a source, vector, and reservoir of mutant and non-mutant SARS-CoV-2 and several other domestic or wildlife animal pathogens (e.g. Aleutian Disease of

mink, avian influenza H5:N1, etc.). Escaped or feral mink could have conservation biology impacts e.g. by spreading SARS-CoV-2 to endangered black-footed ferrets.

*It is time to consider the farmed American mink as an invasive and “injurious species” even in its native North America especially (but not solely) due to its ability to carry and propagate SARS-CoV-2. This is consistent, for example, with how the U.S. Fish and Wildlife Service classified more than a dozen species of native American salamanders as “injurious” due to their propensity to carry an emerging panzootic amphibian infectious disease, the chitrid fungus, caused by the lethal fungus *Batrachochytrium salamandrivorans* (Bsal) (USFWS 2016; Cornell Wildlife Health Lab 2017).*

## ***Supplement 4 - Mutant variants of SARS-CoV-2 from mink***

**1. Background** - A major component of the public health risk from mink SARS-CoV-2 infections is the propensity of mink infections to generate mutant viruses, especially virus variants with mutated spike protein receptor-binding domains (RBD). In this supplement, we briefly review the mutations known to have occurred in mink and their impacts based on several clinical epidemiology and laboratory studies.

### ***2. Abbreviations & definitions***

*ACE2* = Angiotensin-converting enzyme 2 is the host cell target of the SARS-2 RBD. ACE2 sequence variation exists between people and between different animal species. The normal function of ACE2 is to lower blood pressure by causing vasodilation.

*Wuhan-Hu-1/2019* = original human isolate of SARS-CoV-2 and the wild type (WT) strain. SARS-2 RNA sequence mutations are defined by comparison with the RNA and amino acid sequence of this strain as the reference point.

*Bio-layer interferometry (BLI)* = optical label-free bio-sensor technology for measuring biomolecular interactions e.g. the binding affinity between spike protein RBD and the ACE2 host cell receptor.

*Casirivimab & Imdevimab* = therapeutic mAb cocktail made by Regeneron that are FDA Emergency Use Approved to treat mild to moderate symptoms of COVID-19 in non-hospitalized adults and adolescents; given intravenously. The mAbs bind to separate non-overlapping sites of the RBD on the SARS-CoV-2 spike protein. For therapy, the two mAb are combined and administered together to prevent mutational escape. REGN10933 = Casirivimab; REGN10987 = Imdevimab. REGN10933 binds at top of RBD, blocking interaction with ACE2. REGN10987 binds to the side of RBD and does not overlap with the ACE2 binding site.

*Cluster 5* = 2020 Danish mink origin SARS-CoV-2 variant containing five spike protein mutations: H69delta/V70delta/Y453F/I692V/M1229I. Cluster 5 is also called:  $\Delta$ FVI-spike and B.1.1.298. "Delta" means a deleted amino acid; H69delta means a histidine at the 69 position in spike protein is absent.

*Convalescent sera/plasma* = a high fraction of convalescent COVID-19 patients exhibit a neutralizing antibody response directed against the S (spike) protein that may render most of these patients at least temporarily immune to symptomatic reinfection

*GISAID* = Global Influenza Surveillance & Response; Web platform for rapid sharing of data from all influenza viruses and SARS-2 especially whole-genome sequence data.

*hACE2* = human ACE2; the receptor site where SARS-CoV-2 binds to enter host cells

*mAb* = monoclonal antibodies = lab-made proteins that mimic the immune system's ability to fight off harmful pathogens e.g. SARS-CoV-2. Each mAb only binds with one unique epitope on the target antigen. See Casirivimab & Imdevimab above.

*Mutation in RNA sequence* = a change in the nucleotide base in the RNA sequence of the SARS-2 virus. Mutations can involve the substitution of one RNA base to another or the insertion of additional RNA bases or the deletion of existing RNA bases. SARS-CoV-2 mutations are usually defined in comparison to the original Wuhan human isolate which is considered the "non-mutated wild-type" of the virus.

*Mutations in amino acids* = For mutations in the SARS-2 spike protein, one may see, for example, the term Y453F as a common spike protein mutation in mink. It is so named because one amino acid is changed from a Y (tyrosine) to an F (phenylalanine) at position number 453 in the SARS-CoV-2 S (spike) protein.

*pAb* = polyclonal antibodies = a collection of antibodies that recognize multiple epitopes on the same antigen; each antibody recognizes a unique epitope that is located on that antigen.

*Pseudo-virus* = refers to a retrovirus or other virus that can integrate the envelope glycoprotein of another virus (e.g. SARS-CoV-2) to form a chimeric virus with an exogenous (foreign) viral envelope while the genome retains the characteristics of the original retrovirus or other host virus. Pseudo-viruses don't replicate, rendering them harmless. By replacing their surface envelope proteins with those of SARS-CoV-2, researchers can glean insights into the ways the pathogen infects cells. Vesicular stomatitis virus (VSV) from cattle and HIV-based platforms are most common. Chimeric VSV includes the SARS-CoV-2 spike protein and produces a green fluorescent protein as a signal for infection (luciferase is also often used). Pseudo-viruses allow one to work with SARS-CoV-2 at Biosafety level 2 instead of restrictive but necessary Biosafety level 3 or 4 to work with infectious SARS-CoV-2 virions.

*RBD* = receptor-binding domain of SARS-2 spike protein; the RBD attaches the virion to the cell membrane by binding to the viral receptor ACE2, and mediates viral fusion and entry; constitutes the primary target for neutralizing antibodies.

*RBM* = *receptor-binding motif* = main functional motif in the RBD composed of two regions (region 1 and region 2) that form the interface between the S protein and human ACE2. The region outside the RBM also plays an important role in maintaining the structural stability of the RBD.

*Recombination* = during viral replication when host cells are co-infected with different strains of the same virus, the genomes are reshuffled and combined before being packaged and released as new offspring virions, now potentially possessing very different pathogenic properties. Recombination is a crucial factor to consider when developing vaccines and treatments. Recombination of a bat and pangolin coronaviruses in the recent past may have created SARS-CoV-2.

*Remdesivir* = first anti-viral drug FDA-approved to treat COVID-19. Also called Veklury; a broad-spectrum anti-viral drug. Remdesivir is a prodrug that is subsequently bio-transformed into GS-441524 triphosphate, a ribonucleotide analog inhibitor of viral RNA polymerase that prevents new RNA formation.

*SARS-2* = SARS-CoV-2

*Variant* = group of coronaviruses with the same inherited set of very distinctive mutations

*Virion* = the complete infectious form of a virus outside a host cell

*VOC* = SARS-2 variant of concern = virus with mutations of public health concern e.g. escapes vaccine

*Virus neutralization assay* = serological test, usually *in vitro*, to detect the presence and magnitude of functional antibodies that prevent a virus from infecting host cells. The virus is “neutralized” by antibodies if it cannot bind to and infect host cells.

293T (or HEK 293T) = human cell line, derived from the HEK 293 cell line; commonly used for protein expression and production of recombinant retroviruses; used to produce the AstraZeneca COVID-19 vaccine

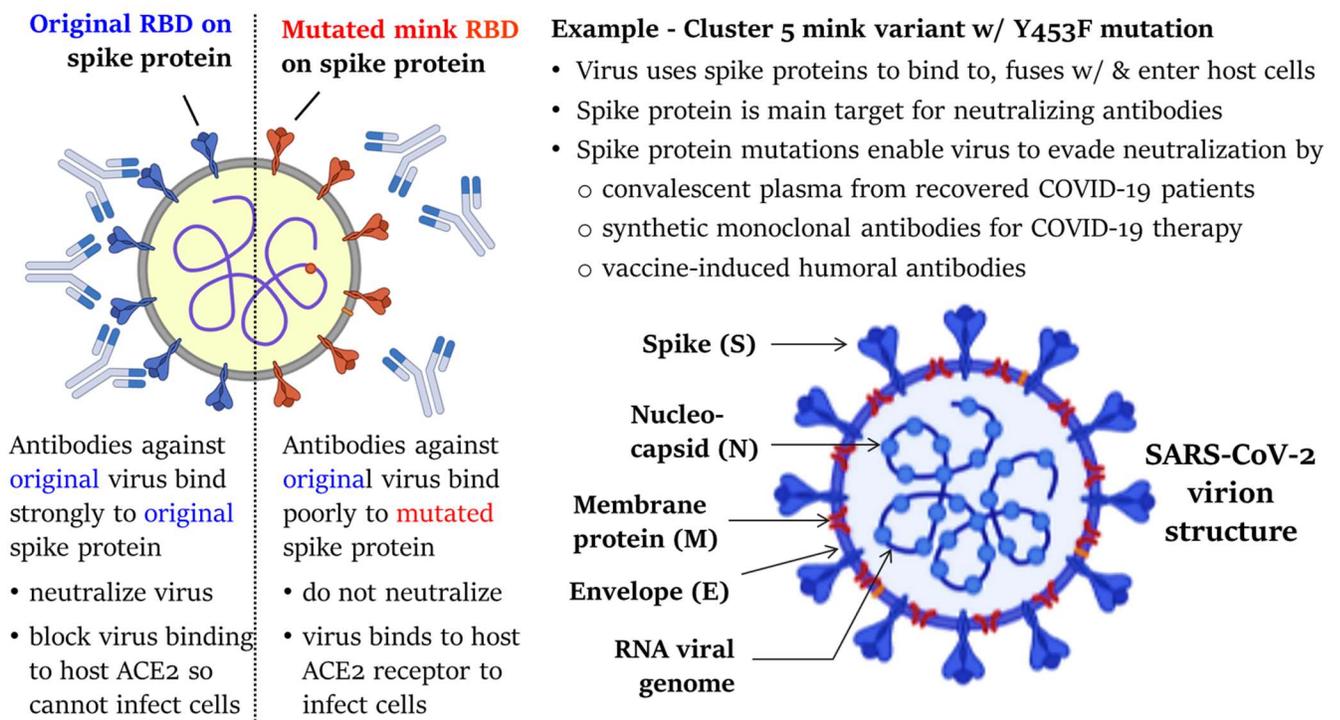
### 3. Methods to assess public health risk from SARS-CoV-2 variants

Some factors to examine to assess the public health risk from a SARS-CoV-2 mutant:

- *In silico* - Virus whole RNA sequence – Any changes in spike protein RBD or RBM?
- *In vitro* - Virus growth kinetics e.g. titer and growth rate
- Biochemistry - Virus binding affinity (chemical bind strength) to human and mink ACE2
- Virus neutralization - by mAbs, convalescent pAb sera, and plasma from vaccinated persons.

**Figure 17** illustrates hypothetical virus neutralization escape by a mink spike protein variant such as Cluster 5.

**Figure 17 - Virus neutralization assay for mink variant with mutated spike protein RBD.**



**4. The SARS-CoV-2 genome and proteins most relevant to mink mutant variants.** The 30 Kb SARS-CoV-2 RNA genome codes for 29 proteins: 25 non-structural (enzyme) proteins, and four structural proteins. However, from epidemiological and public health perspectives, the *spike glycoprotein* and the *RNA-dependent RNA polymerase (RdRp)* are the two most important proteins in SARS-CoV-2. This is because the spike protein receptor-binding domain (RBD) is the meeting point between host cells and viruses. Thus, there is evolutionary pressure on the virus to bind as tightly as possible via the RBD to maximize the chances of infecting a host cell.

The *RdRp* is important because this protein enzyme is responsible for replicating viral RNA as it makes more copies of itself in an infected host cell. Copying errors by the *RdRp* occur at random (loss of fidelity) and result in RNA point mutations or deletions. This is the primary mechanism by which adaptive mutations in the spike protein RBD occur, so the *RdRp* and RBD generate escape mutants in tandem. For unclear reasons, *RdRp* fidelity is further relaxed and diminished in alternative host cell backgrounds and/or virus growth in periods of ecologic stress *e.g.* during farmed mink infections making escape mutants more probable.

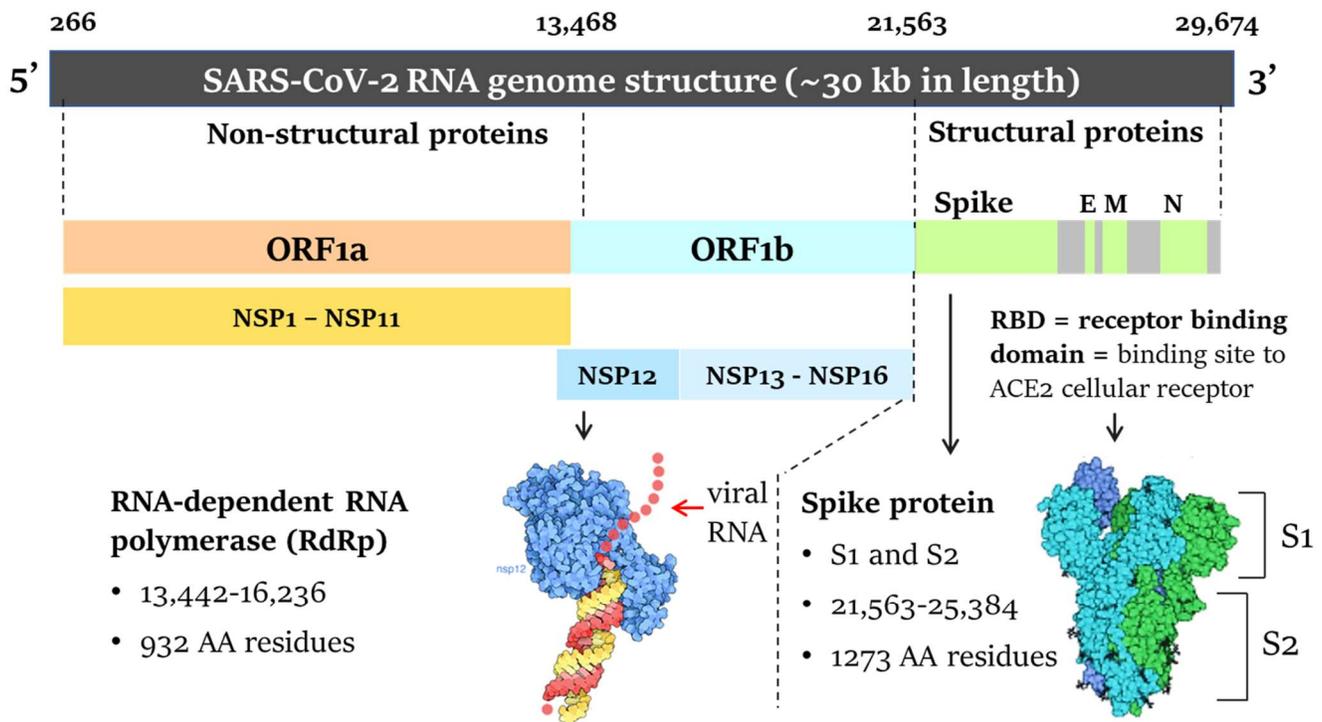
The *RdRp* is also relevant for human drug therapy. The only antiviral drug that is FDA-approved to treat COVID-19 is *Remdesivir* which interferes with the action of the *RdRp* to cause decreased viral RNA production.

The spike glycoprotein is the main target of the immune response against SARS-CoV-2 but also the virus Achilles heel. Neutralizing antibodies target the RBD on the S1 of the spike protein including:

- Convalescent plasma after natural SARS-2 infection
- Therapeutic mAbs *e.g.* Casirivimab & Imdevimab (both FDA-approved as an injectable mAb cocktail)
- Serum antibodies from SARS-CoV-2 vaccinated persons

**Figure 18** shows the genome structure of SARS-CoV-2 emphasizing the *RdRp* and spike proteins.

**Figure 18 - SARS-CoV-2 RNA genome structure and the two most important virus proteins**

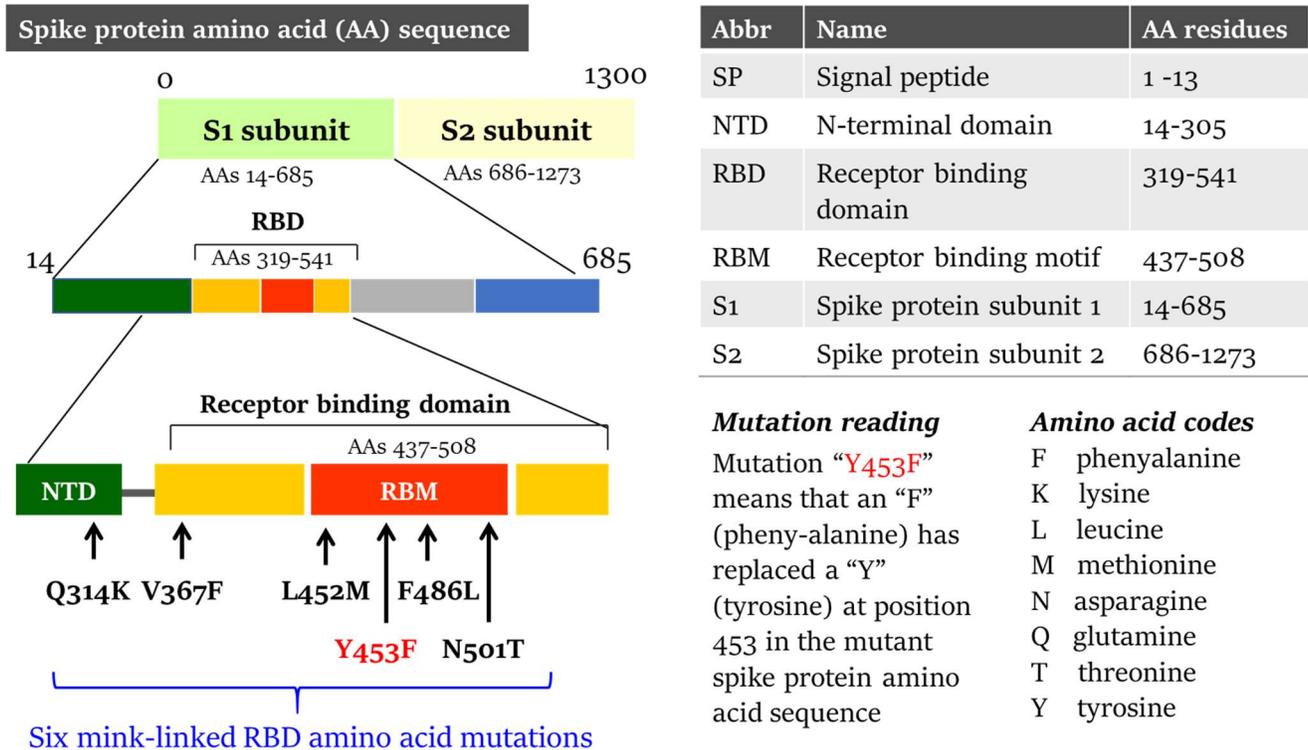


**The two most important SARS-CoV-2 proteins for public health**

- 1 - **RdRp** random RNA copying errors generate mutations
- 2 - **Spike protein RBD** is main target of host immune response so RBD mutations are selected to counter the host

**Figure 19** illustrates the six most frequent amino acid mutations in the spike protein RBD of mink-origin variants.

**Figure 19 - Six amino acid mutations in spike protein RBD common in mink-origin SARS-CoV-2 variants.** RBM = receptor-binding motif = sites of physical contact between RBD and host ACE2 receptor



These six mutations, in particular Y453F, are the best markers of mink-associated SARS-CoV-2 RNA sequences. **Figure 20** provides details of the Cluster 5 variant mutations.

**Figure 20** displays three elements:

- Table with combinations and frequency of mink-associated spike mutations detected in SARS-CoV-2 infected humans in Denmark in 2020.
- Crystal three-dimensional structure of a spike protein trimer with the position of the Y453F variant in the receptor-binding motif and the position of the I692V variant. The regions encompassing the S1147L and M1229I mutations are not within the crystal structure; however, their relative positions are indicated. The position of two amino acids deleted in the N-terminal domain (69-70delHV) is not shown.
- The position of the Y453F variant in a receptor-binding domain complexed with a host ACE2 receptor.

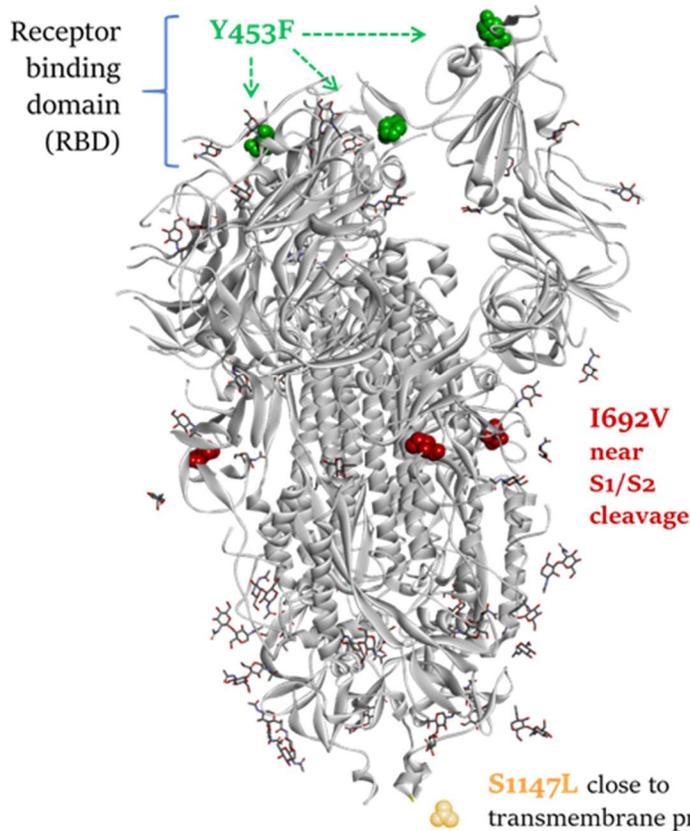
**Figure 20 - The “Cluster 5” mink-associated mutations in the SARS-CoV-2 spike protein.**  
 Modified from Lassaunière et al 2020, p 3; Figures 20B and 20C created by Shi-Hua Xiang

A. Spike mutation combinations*	Abbreviation	No. ** of human clinical sequences
Y445F	F	142
69-70delHV, Y453F	ΔF	162
69-70delHV, Y453F, S1147L	ΔFL	18
69-70delHV, Y453F, 1147L, M1229I	ΔFVI, Cluster 5	12

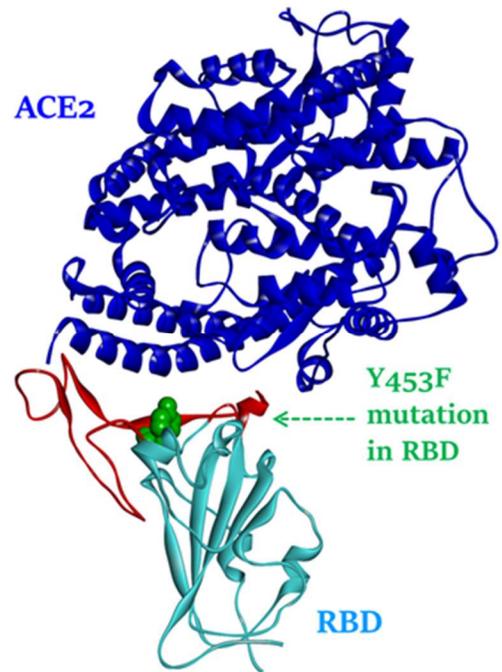
\* All SARS-CoV-2 mink associated sequences contain D614G mutation

\*\* Sequences through 31 Oct 2020

**B. Spike protein trimer 3D structure**



**C. Spike RBD binding with host receptor ACE2**



M1229I in transmembrane protein

**5. Risky mink spike protein N501T mutation:** A recent paper by [Rochman et al 2021](#) in the *Proceedings of the National Academy of Sciences* (PNAS), a top scientific journal, reported that a mink SARS-CoV-2 mutation was observed in farmed mink in Wisconsin and Michigan (USA) that infected people (the N501T spike protein mutation) is among the mutation locations that "... could substantially prolong the pandemic and the vaccination campaign, in which variant-specific vaccines are likely to be required."

**6. Review of the scientific literature on public health risks from mink variants of SARS-2.**

We identified 17 studies (listed in **Table 8**) in which a mink SARS-CoV-2 variant was a major study component. In most studies, the variant of interest was Cluster 5, the mutant strain responsible for the mandatory culling of 17 million farmed mink in Denmark in November 2020. The primary specific mutation of interest was Y543F, one of the five Cluster 5 mink-marker mutations. In **Tables 9A-9G**, we summarize the 16 studies in detail in terms of virus variants, study purpose, technical approach, findings, and interpretation.

**Table 8 - Seventeen studies examining mink-origin SARS-CoV-2 variants (See also Table 9A)**

Sort	Citation	Link	Comments
1	Lassaunière et al 2020. Working paper on SARS-CoV-2 spike mutations arising in Danish mink, their spread to humans, and neutralization data.	<a href="https://files.ssi.dk/Mink-cluster-5-short-report_AFO2">https://files.ssi.dk/Mink-cluster-5-short-report_AFO2</a>	The first report of Danish mink "Cluster 5" mutant; led to a mandated cull of the entire Danish mink herd of 17 million and \$3.1B reimbursement to mink farmers
2	Oude Munnink et al 2021. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans (The Netherlands). <i>Science</i> . 2021 Jan 8;371(6525):172-177.	<a href="https://pubmed.ncbi.nlm.nih.gov/33172935/">https://pubmed.ncbi.nlm.nih.gov/33172935/</a>	Whole-genome sequencing on 16 mink outbreak farms in the Netherlands: virus introduced by humans, evolved; wide-spread mink circulation for weeks; mink virus with unique RNA mutations
3	Welkers et al 2021. Possible host-adaptation of SARS-CoV-2 due to improved ACE2 receptor binding in mink. <i>Virus Evol</i> . 2021 Jan 4;7(1):veaa094.	<a href="https://pubmed.ncbi.nlm.nih.gov/33500787/">https://pubmed.ncbi.nlm.nih.gov/33500787/</a>	Spike protein RBD mutations in mink SARS-2 increase binding affinity to mink ACE2 and human ACE2
4	Bayarri-Olmos et al 2021. The SARS-CoV-2 Y453F mink variant displays a pronounced increase in ACE-2 affinity but does not challenge antibody neutralization. <i>J Biol Chem</i> . 2021 Mar 10. 296:100536.	<a href="https://pubmed.ncbi.nlm.nih.gov/33716040">https://pubmed.ncbi.nlm.nih.gov/33716040</a>	Cluster 5 fitness advantage via receptor adaptation rather than immune evasion; Four-fold higher affinity to hACE2 than the original Wuhan strain; No effect on antibody neutralization
5	Fournier et al 2021. Emergence and outcomes of the SARS-CoV-2 'Marseille-4' variant. <i>Int J Infect Dis</i> . 2021 Mar 27; 106:228-236.	<a href="https://pubmed.ncbi.nlm.nih.gov/33785459">https://pubmed.ncbi.nlm.nih.gov/33785459</a>	French mink SARS-2 spike variant with multiple mutations emerged suddenly; spread worldwide in 2020. May make people sicker vs. non-mutant.
6	Hoffmann et al 2021. SARS-CoV-2 mutations acquired in mink reduce antibody-mediated neutralization. <i>Cell Rep</i> . 2021 Apr 20;35(3):109017.	<a href="https://pubmed.ncbi.nlm.nih.gov/33857422/">https://pubmed.ncbi.nlm.nih.gov/33857422/</a>	Mink SARS-2 spike protein variants are public health risk via reduced antibody protection (escape RBD mutants); the most rigorous study to date on public health risks of mink variants
7	Martin et al 2021. Genetic conservation of SARS-CoV-2 RNA replication complex ... from humans and	<a href="https://pubmed.ncbi.nlm.nih.gov/33549572/">https://pubmed.ncbi.nlm.nih.gov/33549572/</a>	No innate resistance of mink viruses to remdesivir, the only FDA approved anti-viral for COVID-19

Sort	Citation	Link	Comments
	minks suggests minimal pre-existing resistance to remdesivir. <i>Antiviral Res.</i> 2021 Apr;188:105033		
8	Burkholz et al 2021. Paired SARS-CoV-2 spike protein mutations were observed during ongoing SARS-CoV-2 viral transfer from humans to minks and back to humans. <i>Infect Genet Evol.</i> 2021 May 7;93:104897.	<a href="https://pubmed.ncbi.nlm.nih.gov/33971305/">https://pubmed.ncbi.nlm.nih.gov/33971305/</a>	Six common amino acid spike protein RBD mutations in mink SARS-2; Mutations usually occur in pairs, not as singlets; Humans were infected mink with SARS-CoV-2 in the Netherlands, Denmark, U.S. & Canada
9	Zhang et al 2021. Cellular tropism and antigenicity of mink-derived SARS-CoV-2 variants. <i>Signal Transduct Target Ther.</i> 2021 May 17;6(1):196.	<a href="https://pubmed.ncbi.nlm.nih.gov/34001855/">https://pubmed.ncbi.nlm.nih.gov/34001855/</a>	Ten mink variants similar infectivity & cellular tropisms to human viral isolates. Some mink variants with decreased neutralization by some mAb and pAb preparations. Warrants close monitoring of ever-evolving mink viruses
10	Garcia-Beltran et al 2021. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. <i>Cell.</i> 2021 Apr 29;184(9):2372-2383.e9.	<a href="https://pubmed.ncbi.nlm.nih.gov/33743213/">https://pubmed.ncbi.nlm.nih.gov/33743213/</a>	Analyzed sera from 99 people vaccinated with one or two doses of mRNA vaccines against 10 circulating SARS-2 variants. Mink Cluster 5 (B.1.1.298) neutralized by most vaccine sera. Non-mink variants P.1 and B.1.351 had limited vaccine-mediated neutralization.
11	Van Dorp et al 2021. Recurrent mutations in SARS-CoV-2 genomes isolated from mink point to rapid host-adaptation. <i>BioRxiv.</i> Nov 16, 2020 <i>Pre-print</i>	<a href="https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1.full.pdf">https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1.full.pdf</a>	23 recurrent mutations (three nonsynonymous) in mink SARS-2 RBD; independently emerged at least four times but only rarely observed in humans. Three recurrent spike mink RBD mutations are Y453F, F486L, and N501T
12	Tada et al, 2021. Convalescent-phase sera and vaccine-elicited antibodies largely maintain neutralizing titer against global SARS-CoV-2 variant spikes. <i>mBio.</i> 2021 Jun 1:e0069621.	<a href="https://pubmed.ncbi.nlm.nih.gov/34060334">https://pubmed.ncbi.nlm.nih.gov/34060334</a>	Mink origin Cluster 5 RBD mutant was not neutralized by therapeutic mAb REGN10933 (Casirivimab). REGN10987 (Imdevimab) maintained most of its neutralization activity against mink cluster-5 spike proteins. Findings agree w/ Hoffman et al 2021
13	Gobeil et al 2021. Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity. <i>Science</i> 2021 Aug 6;373(6555):eabi6226.	<a href="https://pubmed.ncbi.nlm.nih.gov/33758838/">https://pubmed.ncbi.nlm.nih.gov/33758838/</a>	Mink Y453F mutation in the receptor-binding motif (RBM) improved binding to hACE2; mink spike protein bound well to all antibodies tested
14	Hayashi et al 2020. Effect of RBD (Y453F) mutation in spike glycoprotein of SARS-CoV-2 on neutralizing IgG affinity. <i>BioRxiv.</i> Jan 28, 2021 <i>Pre-print</i>	<a href="https://doi.org/10.1101/2020.11.27.401893">https://doi.org/10.1101/2020.11.27.401893</a>	SARS-2 variants with mink RBD Y453F mutation partially escape detection by four neutralizing mAbs and neutralizing antibodies in serum
15	Motozono et al 2021. An emerging SARS-CoV-2 mutant evades cellular immunity and increases infectivity. <i>Cell Host &amp; Microbe.</i> April 15, 2021.	<a href="https://papers.ssrn.com/sol3/paper.cfm?abstract_id=3827372">https://papers.ssrn.com/sol3/paper.cfm?abstract_id=3827372</a>	Mink Y453F mutants escape HLA-A24-restricted cellular immunity. Mink Y453F induced lower levels of virus-killing interferon-gamma. Y453F mutation increased human ACE2 binding affinity
16	Bazykin GA et al 2021. Emergence of Y453F and Δ69-70HV mutations in a lymphoma patient with long-term COVID-19. <i>Virological.org.</i> Jan 4, 2021.	<a href="https://virological.org/t/emergence-of-y453f-and-69-">https://virological.org/t/emergence-of-y453f-and-69-</a>	SARS-2 in patient w/ lymphoma & chronic clinical COVID-19 gained 18 new mutations over 4 mo.

Sort	Citation	Link	Comments
		<a href="#">70hv-mutations-in-a-lymphoma-patient-with-long-term-covid-19/580</a>	Patient treated w/ immuno-suppressive chemo. Mutations included spike RBD Y453F and Δ69-70HV only found in mink Cluster 5 previously.
17	Ren et al, 2021. Mutation Y453F in the spike protein of SARS-CoV-2 enhances interaction with the mink ACE2 receptor for host adaption. <i>PLoS Pathog.</i> 2021 Nov 8;17(11):e1010053.	<a href="https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1010053">https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1010053</a>	Cluster 5 RBD spike protein mutation Y453F is adaptive; increases virus binding with mink ACE2 receptor without compromising its utilization of human ACE2 receptor. Cluster 5 shows resistance to convalescent sera from COVID-19 patients posing a risk for vaccine development Urgent need to identify potential zoonotic reservoirs and monitor virus evolution in the zoonotic mink host to prevent future outbreaks and develop countermeasures

**Table 9A - Details of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
1	Lassaunière et al 2020	Cluster 5 = DFVI spike = B.1.1.298 D614G = common human clinical isolate similar to Wuhan wild type	Denmark <b>mink</b> farms Molecular epidemiology & outbreak investigation Identity properties & public health risk from <b>mink</b> -origin SARS-2 that spilled back into people in Denmark in fall 2020.	RNA sequence <b>mink</b> SARS-2 Virus neutralization with convalescent sera (pre- <b>mink</b> outbreak) Model virus spike protein structure	Several RBD SARS-2 changes; Increased hACE2 affinity; high viral replication Avg 3.6-fold reduction neutralization vs wild type	Adaption to <b>mink</b> ACE2 <b>Mink</b> variants are serious public health risk Neutralization - just nine human plasma samples
2	Oude Munnink et al 2021	Outbreak isolates Wuhan reference sequence NC_045512.2	Netherlands <b>mink</b> farms Molecular epidemiology & outbreak investigation 16 <b>mink</b> farms - 20K to 75K <b>mink</b>	RNA sequence human & <b>mink</b> outbreak isolates Virus phylogenetics Shoe leather epidemiology	Human & <b>mink</b> sequences almost identical <b>Mink</b> farms - one virus mutation / two weeks	68% of <b>mink</b> farm workers & contacts infected by <b>mink</b> Virus circulated silently many generations on farms
3	Welkers et al 2021	Wild type (non-mutant RBD) Y453F, F486L & N501T	Computational bio-chemistry Molecular model: measure binding energy between SARS-2 spike RBD and ACE2 receptor	Calculated & measured binding energy changes from three <b>mink</b> mutation interactions with human & <b>mink</b> ACE2 receptor	<b>Mink</b> RBD mutations increase binding energy to <b>mink</b> ACE2 & human ACE2 (tighter bond) <b>Mink</b> virus genome surveillance important	<b>Mink</b> SARS-2 strains encode substitutions in genome crucial to ACE2 receptor binding Could potentially affect human neutralizing antibody responses
4	Bayarri-Olmos et al 2021	Cluster-5: Y453F mutation in RBD; origin Dutch <b>mink</b> farms Wuhan-Hu-1/2019 as reference strain	<i>In vitro</i> Biochemistry Mouse vaccine model Compare Cluster-5 vs Wuhan-Hu-1/2019 What are functional properties of <b>Cluster 5 mink</b> variant?	Host cell-virus binding affinity • hACE2-RBD bio-layer interferometry Humoral immunity • ELISA-based hACE2/RBD inhibition assay with human convalescent sera • Mouse vaccine model to assess neutralizing antibody response to each virus strain	Four-fold higher binding affinity to human ACE2 receptor vs Wuhan type strain No effect on antibody neutralization	<b>Cluster 5</b> with enhanced transmission capacity Challenge for SARS-2 control <b>Mink</b> virus fitness advantage via receptor adaptation rather than immune evasion <b>Mink</b> SARS-2 spike variant possibly dangerous to people

**Table 9B - Summary of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
5	Fournier et al 2021	Marseilles-4: 20 mutations; 13 variant hallmarks including S477N in RBD  Likely French <b>mink</b> farm origin; appeared abruptly in June 2020	Molecular epidemiology & outbreak investigation  Compare epidemiological & clinical features of patients infected by Marseilles-4 vs other strains  Determine if Marseilles-4 came from <b>mink</b> farm	Whole genome virus sequencing and cladistic analysis of 1038 SARS-2 isolates  qPCR assay developed for Marseilles-4 strain  Identify mutations	Marseilles-4: caused 2106 & 12-100% of SARS-CoV-2 infections in Marseilles from Sept 2020  Emerged suddenly and spread worldwide in 2020  Re-infected 11 patients previously infected with a different SARS-2 strain  More frequent hypoxia vs other strains among sick  Isolated from French <b>mink</b> farm in Nov 2020	Reinfection due to either short-term protective immunity or lack of cross-immunity from different SARS-2 strains  Remdesivir or hyper-immune plasma therapy generate & select mutant variants  <b>Mink</b> farm generated SARS-2 variants may cause human epidemics
6	Hoffmann et al 2021	Five SARS-2 variants  hCoV-19/Wuhan/Hu-1/2019 (human WT; control)  D614G dominant (human-to- <b>mink</b> ; common RDB mutant; reference)  Y453F <b>mink</b> RBD mutant ( <b>mink</b> -to-human strain)  D614G & Y453F ( <b>mink</b> -to-human)  D614G+H69D/V70D/Y453F (Cluster 5; <b>mink</b> -to-human)	<i>In vitro</i>  Molecular virology  Do spike proteins with <b>mink</b> RBD mutation Y453F (alone or with other mutations) show altered  • binding to human cells? or  • susceptibility to antibody-mediated neutralization?  Does <b>mink</b> Y453F mutation cause changes in spike protein expression, altered binding to host cell receptor or susceptibility to neutralizing antibodies?	Create vesicular-stomatitis-virus (VSV) reporter particles bearing various SARS-2 spike proteins (SARS-2 VSV pseudo-virus)  For each spike protein variant, assess human host cell entry & its inhibition with  • Exogenous ACE2  • Two therapeutic mAbs  • Animal pAbs &  • SARS-2 human convalescent sera or plasma	Mutated <b>mink</b> SARS-2 spike proteins enter human cells efficiently & are inhibited by soluble ACE2  <b>Mink</b> RBD mutant Y453F: <b>reduces neutralization</b> by mAb Casirivimab & “immune” sera/plasma from COVID-19 patients  100% neutralized by mAb Imdevimab  <b>Reduced inhibition</b> by most serum/plasma samples with variable efficiency	<b>Mink</b> RBD mutants reduced efficacy of both natural and therapeutic antibodies.  Human antibody responses to infection or mAbs used for treatment may not protect against SARS-2 RBD <b>mink</b> variants  Infected <b>mink</b> can compromise viral inhibition by human antibodies induced by SARS-2 infection or under development for COVID-19 treatment.

**Table 9C - Summary of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
7	Martin et al 2021	NA	<p>Remdesivir (RDV) is only antiviral drug approved for treatment of COVID-19.</p> <p><i>In silico</i> sequence analysis of <a href="#">mink</a> &amp; human isolates</p> <p>Analyze human &amp; <a href="#">mink</a> RNA sequences for genetic diversity in RNA replication complex (nsp7, nsp8, nsp10, nsp12, nsp13, and nsp14);</p>	<p>&gt;90,000 SARS-CoV-2 sequences from globally circulating human clinical isolates</p> <p>Included recently emerged UK &amp; S Africa variants, and</p> <p>&gt;300 from <a href="#">mink</a> isolates</p> <p>Focus on RNA-dependent RNA polymerase (nsp12), the molecular target of RDV</p>	<p>Low genetic variation: only 12 amino acid substitutions present in entire RNA replication complex in <math>\geq 0.5\%</math> of analyzed sequences in human clinical isolates</p> <p>Low sequence variation in RNA replication complex also observed in <a href="#">mink</a> isolates.</p> <p>Low diversity &amp; high genetic stability of RNA replication complex over time &amp; in recently emerged SARS-2 variants</p>	<p>Minimal global risk of pre-existing SARS-CoV-2 resistance to RDV.</p> <p>Transmission of SARS-CoV-2 from humans to other species and back may introduce genetic diversity; Should monitor for emergence of changes that could impact efficacy of therapeutics &amp; vaccines.</p>
8	Burkholz et al 2021	<p>SARS-CoV-2 reference sequence WIVo4 (MN996528.1)</p> <p>SARS-CoV-1 reference sequence (NC_004718.3)</p> <p>235K SARS-2 spike protein sequences from across globe</p>	<p><i>In silico</i></p> <p>Identify mutations in <a href="#">mink</a>-associated SARS-2 isolates</p> <p>Analyze spike protein mutations in RBD associated with spread of SARS-CoV-2 from humans to <a href="#">mink</a> and back to human worldwide by sequence alignment</p> <p>After filtering 782 human &amp; 251 <a href="#">mink</a> sequences remained for analysis</p>	<p>Bioinformatics</p> <p>Computational biology to visualize 3D structure of human &amp; <a href="#">mink</a> RBD and ACE2; model binding affinities</p> <p>Align <a href="#">mink</a> &amp; human ACE2 sequences</p> <p>Phylogenetic tree of human and <a href="#">mink</a> RBD sequences</p> <p>Plot mutation frequency by geography, date &amp; species to find patterns of zoonotic transfer</p>	<p>Six common amino acid RBD mutations in <a href="#">mink</a> SARS-2</p> <p>Mutations usu in pairs not single; pairing is functional</p> <p>Humans &amp; <a href="#">mink</a> have up to 92% amino acid sequence similarity in ACE2 proteins</p> <p>Of ACE2 residues that interact with RBD of spike, <a href="#">mink</a> &amp; human 83% similar</p> <p>Antibody-based therapeutics &amp; spike protein vaccines depend on stable RBD AA sequence to generate neutralizing antibody</p> <p>Affinity minimally affected when <a href="#">mink</a> ACE2 residues substituted for human ACE2</p>	<p>Humans infected with SARS-CoV-2 infected <a href="#">mink</a> populations in the Netherlands, Denmark, United States &amp; Canada.</p> <p>SARS-2 <a href="#">mink</a> isolates with mutation sets in spike protein RBD often occur in specific combinations &amp; are transferred back into humans</p> <p>Close attention to viral transfer from humans to farm animals and pets required to prevent build-up of a viral reservoir for potential future zoonotic transfer</p>

**Table 9D - Summary of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
9	Zhang et al 2021	Ten <b>mink</b> pseudo-viruses carrying spike protein mutations created:  Human D614G as common RBD variant (control)  Y453F; Y453F+69-70del; Y453F+69-70del+I692V+M1229I ( <b>cluster 5 variant</b> ); Y453F+69-70del+S1147L; Y453F+G614D; Y453F+G261D+G614D: F486L; F486L+L452M; F486L+A262S+Q314K; A262S.	<i>In silico</i> - <b>Mink</b> SARS-2 sequence analysis  Compare common human D614G variant whole genome sequence with 10 <b>mink</b> pseudo-viruses  <i>In vitro</i>  Virus neutralization  Purpose: analyze species tropism and antigenicity of spike protein of ten <b>mink</b> variants using pseudo-virus-based assays in 25 cell lines and 293T cells expressing ACE2 receptor from 14 species	Analyze 338 <b>mink</b> SARS-2 sequences in GISAID <ul style="list-style-type: none"><li>• 13 <i>Mustela lutreola</i></li><li>• 325 <i>Neovison vison</i></li></ul> <i>In vitro</i> - Assess species tropism (infectivity) of spike protein of ten <b>mink</b> variants with pseudo-virus assays on <ul style="list-style-type: none"><li>• 25 cell lines from 10 animal species</li><li>• 293T cells expressing ACE2 receptor from 14 animal species</li></ul> Assess antigenicity (virus neutralization) of ten <b>mink</b> variants for reactivity with: <ul style="list-style-type: none"><li>• 17 mAbs against RBD</li><li>• PAbs from animals</li><li>• Convalescent plasma of COVID-19 patients</li></ul>	Nine mutations (69-70del, G261D, A262S, Q314K, L452M, Y453F, F486L, I692V, M1229I, along with D614G) found in spike protein of <b>mink</b> variants  No significant change in cell tropisms (infectivity) in <b>mink</b> variants vs control virus  Slight increase of infectivity in 69-70del and A262S-containing <b>mink</b> variants  Significantly reduced infectivity of <b>Cluster 5</b> variant  Neutralizing mAbs assays: <b>mink</b> variants with Y453F, F486L & A262S with decreased reactivities to at least one therapeutic mAb  F486L variants resistant to eight mAbs + some PAb anti-sera or convalescent plasma	<b>Mink</b> variants similar to human viral isolates in infectivity & cellular tropisms  <b>Mink</b> variants with F486L in conjunction with other mutations have decreased neutralization by some mAbs and polyclonal antibody preparations  <b>Mink</b> variants warrant close monitoring
10	Garcia - Beltran et al 2021	Ten globally circulating SARS-2 w/ spike mutations:  Wild type Wuhan: MN908947.1  D614G: China now global dominant  B.1.1.7: UK VOC  B.1.1.298: Denmark <b>mink Cluster 5</b>  B.1.429: CA VOC  P1 & P2: Brazil & Japan VOCs  B.1.315 v1, v2, v3: South African VOCs	<i>In vitro</i> vaccine efficacy  Purpose: Assess virus neutralization of sera from individuals who received one or two doses of BNT162b2 (Pfizer) or mRNA-1273 (Moderna) mRNA vaccines against SARS-2 pseudo-viruses that bear spike proteins on circulating strains.  Controls: SARS-CoV from 2002 Hong Kong outbreak & pre-emergent bat-derived WIV1-CoV	Phylogenetic tree: RNA sequence analysis to identify global SARS-2 variants of concern (VOCs) and their mutations  Sera from cohort of 99 individuals who received either one or two full doses of the BNT162b2 or mRNA-1273 vaccines  Luminescence-based lentiviral pseudo-virus neutralization assay  Compare pseudo-virus neutralization titers	A relatively small number of mutations can mediate potent escape from vaccine responses  Most mutations in spike S1 & RBD  Five of 10 pseudo-viruses, harboring RBD mutations, including K417N/T, E484K and N501Y, were highly resistant to neutralization  Danish <b>mink</b> variant B.1.1.298 (Y453F) exhibited neutralization generally similar to that of wild-type and parental D614G variant	BNT162b2 and mRNA-1273 vaccines achieve only partial cross-neutralization of novel variants  This supports reformulation of existing vaccines to include diverse spike sequences  Development of new vaccines capable of eliciting broadly neutralizing antibodies is necessary to resolve ongoing pandemic

**Table 9E - Summary of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
11	Van Dorp et al 2021	Whole genome SARS-2 sequences: 239 from mink in Denmark & The Netherlands; 58,803 human from across the globe; Wuhan reference sequence	Computational virology RNA sequence analysis A non-synonymous substitution is a nucleotide mutation that alters the amino acid sequence of a protein Model ACE2 binding to <b>mink</b> SARS-2 mutants	Bioinformatics; phylogeny Screen SARS-2 <b>mink</b> genomes for recurrent mutations Predict role of <b>mink</b> SARS-2 RBD mutations on binding stability of human & <b>mink</b> spike-ACE2 complex	23 recurrent mutations (three nonsynonymous) in <b>mink</b> SARS-2 RBD; independently emerged at least four times but only rarely observed in humans Three recurrent spike <b>mink</b> RBD mutations are Y453F, F486L and N501T	Repeat emergence of mutations of the virus isolated from <b>mink</b> in Denmark & Netherlands points to ongoing rapid adaptation of SARS-2 to a new <b>mink</b> host Binding stability of <b>mink</b> mutants similar with human or <b>mink</b> ACE2 as receptor
12	Tada et al 2021	Five variant SARS-2 • D614G: most prevalent variant in world • B.1.351 South African VOC • B.1.1.7 UK VOC • <b>Mink Cluster 5</b> from Denmark • COH.20G/677H Columbus OH	<i>In vitro</i> Molecular virology Do two FDA-approved mAbs to treat SARS-2 neutralize five SARS-2 “variants of concern” (VOCs)	Produce two therapeutic mAbs in lab Test mAb REGN10933 and mAb REGN10987 for ability to neutralize five SARS-CoV-2 variants Measure neutralizing activity with lentiviral pseudo-type virions expressing each of the five variant spike proteins	REGN10987 (Imdevimab) maintains most of its neutralization activity against viruses with B.1.1.7, B.1.351 and <b>mink cluster-5</b> spike proteins REGN10933 (Casirivimab) lost neutralization activity against B.1.351 & <b>cluster 5</b> Failure to neutralize <b>mink</b> cluster-5 spike protein is caused by Y453F mutation.	Findings for Imdevimab & Casirivimab agree with Hoffman et al 2021  Highlights need to identify antibodies against highly conserved spike protein epitopes which virus cannot readily mutate
13	Gobeil et al 2021	RNA sequence of four spike variants of concern (VOC): • B.1.1.7 (UK) • B.1.1.28 (Brazil) • B.1.351 (SA) • <b>Cluster 5 mink</b>	Antigenic and structural impacts of the spike (S) protein mutations from four variants,	Purified spike protein of each VOC; Binding of spike protein to recombinant hACE2 (ELISA) Binding affinity to antibody panels	All variants either retained or improved binding to the ACE2 receptor <b>Mink</b> Y453F substitution in receptor binding motif (RBM) improved binding to hACE2 <b>Mink</b> spike protein bound well to all antibodies tested	Risk from <b>mink</b> : virus will evolve & acquire new mutations & transmit back to humans New <b>mink</b> variants could be resistant to vaccines and therapies

**Table 9F - Summary of studies of mink SARS-CoV-2 mutant variant**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
14	Hayashi et al 2020 <a href="#">Pre-print</a>	Mink RBD Y453F Wild type Wuhan RBD (control)	Investigate: Characteristics of SARS-CoV-2 RBD Y453F mutant with 3D structural analysis Binding of RBD Y453F to hACE2 and mAb panel Effect of SARS-2 RBD Y453F mutant on neutralizing antibodies in serum derived from COVID-19 positive patients	<i>In vitro</i> Express wild type RBD & RBD Y453F recombinant proteins in HeLa cells Assay binding of spike glycoprotein Y453F mutant to hACE2 Determine affinity of spike glycoprotein Y453F mutant to six neutralizing monoclonal antibodies using 3D protein structure modeling & protein docking analysis	Y453F mutation did not affect 3D structure of conventional SARS-CoV-2 spike glycoproteins Binding of Y453F mutant to human ACE2 slightly weaker vs conventional spike glycoprotein Affinity between Y453F mutant and four of six mAbs (CC12.1, CC12.3, COVA2-39, COVA2-04, CV07-250, CV07-270) examined clearly weak vs. conventional spike glycoprotein No affinity for RBD Y453F in serum IgG of 19 of 21 COVID-19-positive patients	Natural selection “adaptation” in the coronavirus can occur during coronavirus amplification in vivo in farmed <a href="#">minks</a> Y453F mutation causes loss of neutralizing antibody on binding between ACE2 and RBD SARS-2 variants with RBD Y453F partially escape four neutralizing mAbs and neutralizing serum
15	Motozono et al 2021	Two SARS-CoV-2 spike proteins L452R (B.1.427/429) Y453F (B.1.298)	Humoral immunity to SARS-2 variants has been studied Human leukocyte antigen (HLA)-restricted cellular immunity is unaddressed Cyto-toxic T-lymphocytes (CTLs) recognize non-self epitopes on virus-infected cells via human leukocyte antigen (HLA) class I molecules CTL-mediated antiviral immunity is HLA restricted	<i>In vitro</i> Molecular virology SARS-2 variants: L452R and Y453F mutations both in spike protein receptor binding motif (RBM) Yeast expressing human ACE2 to assess mutant RBM binding HIV-1-based reporter pseudo-virus to assess mutant RBM infectivity GISAID database search to determine frequency of Y453F mutations	Y454F & L452R mutations increase spike protein stability Levels of anti-viral interferon gamma (INF- $\gamma$ ) induced by Y453F & L452R much less vs wild type RBD Y453F mutation significantly increased hACE2 binding affinity Infectivity of Y453F mutant significantly lower than parental spike protein with pseudo-virus Y453F mutation found in 1,274 SARS-2 sequences in humans, cats & <a href="#">mink</a>	Y453F mutants escape HLA-A24-restricted cellular immunity HLA-A24 restricted cellular immunity potentially affects evolution of viral phenotypes Escape from cellular immunity is a further threat from SARS-2 HLA-restricted CTLs may play crucial roles in controlling SARS-CoV-2 infection and COVID-19

**Table 9G - Summary of studies of mink SARS-CoV-2 mutant variants**

Sort	Study	Virus variants	Study type & purpose	Technical approach	Findings	Interpretation
16	Bazykin et al 2021	Russian 44 year old woman patient with lymphoma & chronic COVIS-19 SARS-2 isolates collected over four month in mid-2020 with 18 total mutations Wuhan-Hu-1/2019: reference strain to define mutations	Case study Genetic epidemiology Genomic analysis of SARS-CoV-2 from an immunosuppressed (from chemotherapy) lymphoma patient with long-term COVID-19. Persistently positive by PCR for SARS-2	Viral phylogeny Whole genome sequencing of serial patient SARS-2 isolates to detect mutations Patient S, female, aged 47, diagnosed with non-Hodgkin diffuse B-cell lymphoma IV stage B, treated with immunosuppressive chemotherapy Search GISAID (SARS-2 sequence database)	Independent gain of 18 new mutations over 4 months of COVID-19 clinical disease Mutations included spike RBD Y453F and Δ69-70HV mutations found in <a href="#">mink Cluster 5</a> Patient's lineage not related to <a href="#">mink cluster</a> so these mutations were gained anew As of 1.4.2021, patient S represents only sample in GISAID with combination of S:Y453F and S:Δ69-70HV mutations outside of <a href="#">mink Cluster 5</a> 25 genetic changes distinguish the patient S sample from Wuhan-Hu-1/2019 reference	Persistent COVID-19 positive patients usually have suppressed immune systems SARS-CoV-2 lineage of patient S underwent rapid evolution within the host; many variants present at same time Patient findings show consistent effect of mutations on hACE2 binding and/or antibody avoidance Long term immunosuppression generates many SARS-2 mutants
17	Ren et al 2021	Wild type SARS-2 Cluster 5 mink SARS-2 Serum from ten COVID-19 recovered patients	<i>Investigate:</i> Public health implications of the <a href="#">Cluster 5</a> mutations on diagnostics, therapeutics and vaccine development Characteristics of SARS-CoV-2 RBD Y453F mutant with 3D structural analysis Binding of RBD Y453F to hACE2 and mink ACE2 Effect of SARS-2 RBD Y453F mutant on neutralizing antibodies in serum from COVID-19 positive patients	<i>In silico &amp; in vitro approaches</i> Sequence analysis Express wild type RBD & RBD Y453F recombinant proteins in HeLa cells using lentiviral vector Assay binding of spike glycoprotein Y453F mutant to hACE2 & mink ACE2 Surface plasmon resonance Crystal structure of SARS-CoV-2 Y453F RBD bound to mink ACE2 Pseudovirus neutralization assay	The <a href="#">Cluster 5</a> spike Y453F mutation is an adaptive It enhances binding to mink ACE2 and other orthologs of <i>Mustela</i> species without compromising, and even enhancing, its ability to utilize human ACE2 as a receptor for virus entry into host cells <a href="#">Cluster 5</a> Y453F mutation is essential and sufficient for enhanced binding with mink ACE2	This study provides critical insights into SARS-2 adaption and evolution Highlights importance of surveillance of viral variants in animals to reduce risk of emergence of new viral variants & to prevent future outbreaks Data demonstrate that the mink SARS-CoV-2 spike protein evolved to escape neutralization by convalescent serum but still remains sensitive to an ACE2-based therapeutic strategy

## Supplement 5 - Cited references & image credits

(Annotations in green italic font)

Table 10 - References cited by the information source

Color code	Meaning	Example	Count	Percent
Uncolored	Peer-reviewed report	<i>Science</i>	79	58%
Yellow	General media	<i>New York Times</i>	22	16%
Light blue	Science media	<i>Live Science</i>	17	12%
Light purple	Mink industry	American Mink Exchange	5	4%
Light pink	Government or agency	USDA, CDC, WHO, OIE	12	9%
Light grey	Book	Univ Missouri Press	2	1%
<b>Totals</b>			<b>137</b>	<b>100%</b>

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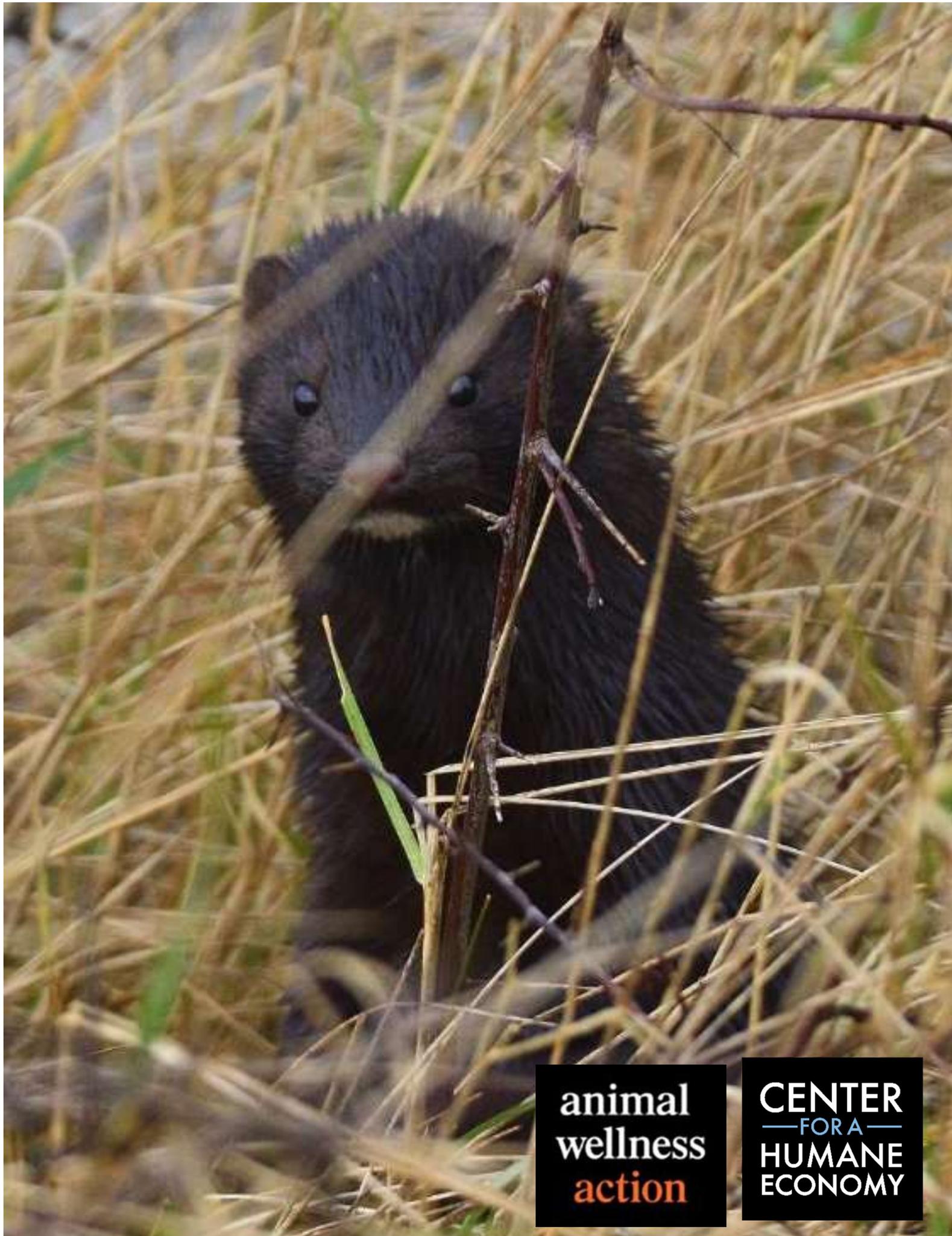
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2	Back cover	Wild American mink	Tom Lee	<a href="https://www.flickr.com/photos/68942208@No2/39987519141">https://www.flickr.com/photos/68942208@No2/39987519141</a>	CC BY-NC-ND 2.0
3	Fig 2, p 16	Mink distribution map	Osado	<a href="https://en.wikipedia.org/wiki/American_mink#/media/File:Mapa_Neovison_vison.png">https://en.wikipedia.org/wiki/American_mink#/media/File:Mapa_Neovison_vison.png</a>	Public domain
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14	Box 3, p 37	Mink restraint	FCUSA	<a href="https://furcommission.com/mink-farming-2/">https://furcommission.com/mink-farming-2/;</a> <a href="https://youtu.be/WwPsStvktks">https://youtu.be/WwPsStvktks;</a> (screen grab)	Not copyrighted; Fair use claim
15	Fig 10A, p 45	Map of CWD	USGS	<a href="https://www.usgs.gov/media/images/distribution-chronic-wasting-disease-north-america-0">https://www.usgs.gov/media/images/distribution-chronic-wasting-disease-north-america-0</a>	Public domain
16	Box 5, p 47	Eurasian mink	Martin Mecnarowski	<a href="https://image.shutterstock.com/image-photo/close-photo-pair-european-minks-60ow-341819801.jpg">https://image.shutterstock.com/image-photo/close-photo-pair-european-minks-60ow-341819801.jpg</a>	Purchased Shutterstock license
17	Box 5, p 47	Wild American mink	Andrew Reding	<a href="https://www.flickr.com/photos/11802018@No7/18866041822">https://www.flickr.com/photos/11802018@No7/18866041822</a>	CC BY-NC-ND 2.0

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20	Fig 14A, p 54	Wild mink	Jen Goellnitz	<a href="https://www.flickr.com/photos/goellnitz/34748964153/in/album-72157682396922681/">https://www.flickr.com/photos/goellnitz/34748964153/in/album-72157682396922681/</a>	CC BY-NC 2.0
21	Fig 14A, p 54	Wild mink head	Gouldingen	<a href="https://wanderlord.com/wp-content/uploads/2019/07/Scandinavian-mink.jpg">https://wanderlord.com/wp-content/uploads/2019/07/Scandinavian-mink.jpg</a>	Wikipedia public domains
22	Fig 14A, p 54	Domestic mink Grey, heavy set	Konstantin Sokolov1973	<a href="https://www.shutterstock.com/image-photo/wild-gray-mink-light-box-1585533325">https://www.shutterstock.com/image-photo/wild-gray-mink-light-box-1585533325</a>	Purchased Shutterstock license
23	Fig 14B, p 55	Aerial view of large Wisconsin mink farm	NA	NA	Google Earth
24	Fig 14B, p 55	Wild mink riverine habitat in Oregon	Bureau of Land Management	<a href="https://www.flickr.com/photos/blmoregon/15319361164/in/photolist-pkHJmC-7XybHq-unB3XZ-XfERNE-2kf3zH3-bibEGg-aATicu-8zX17W-bTd7Cz-WeKUvu-zf2bc-cJWkgU-9wPh1v-2c3T46V-u62pNU-tqApzb-tqL5ZK-7xwEx9-p8hfX9-oQPNyk-agvMdx-fDYTbi-6rhYm-avkpGN-5XhLy2-q1gyi4-oQPBK9-XrwLmb-fk2K2y-fbsUpS-hS2ywj-8GnQez-oQPkM7-7XyccN-oQPzoq-pkXeKa-QDe1S6-Xvxx4c-64NyzF-7nHCkj-baVXbP-qfqKks-eRdkkX-qhDBd5-6yNcGM-fmm9hq-feiruK-2imcw22-7mh2L-2ejW6X9">https://www.flickr.com/photos/blmoregon/15319361164/in/photolist-pkHJmC-7XybHq-unB3XZ-XfERNE-2kf3zH3-bibEGg-aATicu-8zX17W-bTd7Cz-WeKUvu-zf2bc-cJWkgU-9wPh1v-2c3T46V-u62pNU-tqApzb-tqL5ZK-7xwEx9-p8hfX9-oQPNyk-agvMdx-fDYTbi-6rhYm-avkpGN-5XhLy2-q1gyi4-oQPBK9-XrwLmb-fk2K2y-fbsUpS-hS2ywj-8GnQez-oQPkM7-7XyccN-oQPzoq-pkXeKa-QDe1S6-Xvxx4c-64NyzF-7nHCkj-baVXbP-qfqKks-eRdkkX-qhDBd5-6yNcGM-fmm9hq-feiruK-2imcw22-7mh2L-2ejW6X9</a>	CC BY 2.0
25	Fig 14B, p 55	White mink in a cage	Lynsey Grosfield	<a href="https://www.shutterstock.com/editor/image/farmed-american-mink-383860666">https://www.shutterstock.com/editor/image/farmed-american-mink-383860666</a>	Purchased Shutterstock license
26	Fig 14B, p 55	Wild mink and burrow along a stream	Christian Fischer	<a href="https://commons.wikimedia.org/wiki/File:NeovisonVison.jpg">https://commons.wikimedia.org/wiki/File:NeovisonVison.jpg</a>	Creative Commons International
27	Fig 14B, p 55	Crowded white mink in pen	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/36487141@No2/3365101125">https://www.flickr.com/photos/36487141@No2/3365101125</a>	CC BY-NC-SA 2.0
28	Fig 14B, p 55	Wild mink swimming	George Gentry	<a href="https://www.flickr.com/photos/myfwc/50134206462/in/photolist-2jobUW3-CN7dBD-2jo7USK-IMFFY3-2jo7Vfy-2joaLQu-doLygR-s3ThyL-dBnmQ6-drX48F-6ZuSzC-2xqbA-oeVGF4-2kSxMMr-dXjTwp-aBnWR2-PmauFd-2kWdgB6-9keBsN-9hYPzX-9keBp1-tRr8wM-2ecZvBQ-2kTr6md-2hsvRTz-2i5dcuB-ksPBeP-zihFufK-2gsrxgV-2k4ijyP-HuPrh-2jMX5qD-2dVwJKg-RtdVwt-RXPGQB-cTLxqs-2jo7Wiv-2joaCTY-2joaLZc-UrwEMN-FjBne4-puHDoL-Uua5Dj-ReDn58-eALy5A-2e6xVvH-23pKNYt-eBcHgg-i2fBdm-5pR61">https://www.flickr.com/photos/myfwc/50134206462/in/photolist-2jobUW3-CN7dBD-2jo7USK-IMFFY3-2jo7Vfy-2joaLQu-doLygR-s3ThyL-dBnmQ6-drX48F-6ZuSzC-2xqbA-oeVGF4-2kSxMMr-dXjTwp-aBnWR2-PmauFd-2kWdgB6-9keBsN-9hYPzX-9keBp1-tRr8wM-2ecZvBQ-2kTr6md-2hsvRTz-2i5dcuB-ksPBeP-zihFufK-2gsrxgV-2k4ijyP-HuPrh-2jMX5qD-2dVwJKg-RtdVwt-RXPGQB-cTLxqs-2jo7Wiv-2joaCTY-2joaLZc-UrwEMN-FjBne4-puHDoL-Uua5Dj-ReDn58-eALy5A-2e6xVvH-23pKNYt-eBcHgg-i2fBdm-5pR61</a>	CC BY-NC-ND 2.0

Sort	Location	Description	Credit	Source or weblink	License
29	Fig 14C, p 56	Feed wagon on Wisconsin mink farm	Sara Stathas	<a href="https://sarastathas.photoshelter.com/download-page/DoouooHaLKrjUxLI">https://sarastathas.photoshelter.com/download-page/DoouooHaLKrjUxLI</a>	Permission to use was granted by Sara Stathas on 6.8.21
30	Fig 14C, p 56	Mink farm wet-cat food-like feed on cage tops	Marcin Hernik	<a href="https://www.flickr.com/photos/151621525@N07/32574629626/in/photolist-RCvuvh-2xakfs-XXdz8-2jouc82-RG5KMV-R7zNcq-2ka46t6-2ka3H9R-4ceKQh-bEj3BW-2k9YQ28-bEjfMm-bEjes5-bTdCAC-bTdzWV-2ka46bn-2ka466C-bTdQ8c-2ka3Gys-bEiKhL-2ka468m-2jouc5m-2ka3GJn-bEjdUd-2k9YPEM-2ka3GUC-bTdNJZ-2k9YQPB-bTdThD-bTd8vV-2k9YXML-bEiBEY-bTdH7D-2ka46GN-bTdK8k-bTdSo2-bEjaXf-bEiik5-a4hXBW-bEj4d7-bTd4Fk-bEiZhf-2k9YPGW-2k9YQ11-bTdCvk-bEjNN-bTdVzz-bTdPMT-bTdKZa-bTdRWg">https://www.flickr.com/photos/151621525@N07/32574629626/in/photolist-RCvuvh-2xakfs-XXdz8-2jouc82-RG5KMV-R7zNcq-2ka46t6-2ka3H9R-4ceKQh-bEj3BW-2k9YQ28-bEjfMm-bEjes5-bTdCAC-bTdzWV-2ka46bn-2ka466C-bTdQ8c-2ka3Gys-bEiKhL-2ka468m-2jouc5m-2ka3GJn-bEjdUd-2k9YPEM-2ka3GUC-bTdNJZ-2k9YQPB-bTdThD-bTd8vV-2k9YXML-bEiBEY-bTdH7D-2ka46GN-bTdK8k-bTdSo2-bEjaXf-bEiik5-a4hXBW-bEj4d7-bTd4Fk-bEiZhf-2k9YPGW-2k9YQ11-bTdCvk-bEjNN-bTdVzz-bTdPMT-bTdKZa-bTdRWg</a>	CC BY-SA 2.0
31	Fig 14C, p 56	Farm mink feeding from cage tops	FCUSA	<a href="https://furcommission.com/mink-farming-2/">https://furcommission.com/mink-farming-2/;</a> <a href="https://youtu.be/WwPsStvktks;">https://youtu.be/WwPsStvktks;</a> (screen grab)	Not copyrighted; Fair use claim
32	Fig 14C, p 56	Wild mink with fish	John McAvoy	<a href="https://theconversation.com/nowhere-to-hide-as-the-hunt-for-unwelcome-mink-goes-digital-19125">https://theconversation.com/nowhere-to-hide-as-the-hunt-for-unwelcome-mink-goes-digital-19125</a>	Creative Commons public domain
33	Fig 14C, p 56	Wild mink with a garter snake	Eric Bégin	<a href="https://www.flickr.com/photos/ericbegin/3952002334/">https://www.flickr.com/photos/ericbegin/3952002334/</a>	CC BY-NC-ND 2.0
34	Fig 14C, p 56	Wild mink with mouse	Mike Kestell	<a href="https://www.flickr.com/photos/38409567@N07/49748326211/in/photolist-2iN6bbg-2k55VKF-ynKeQG-2k47HeR-2cKyEDR-q53CKq-2jYYMqS-298VYBc-2kPHaaM-4NmPKu-2iEMPjK-2kPMbZE-2kdzaUZ-5MExQj-deqvR2-63ubu6-24hz7Gk-4ZZAco-Q1GS07-2jL5s2s-bB21mU-2c7r6w8-Pvbb4N-22yemc4-4DGQ9C-2kE3jYp-SDNQKx-2jmCuJA-51Wf9j-oPvmLE-EKfzs-zvPs5r-2i8pjoh-ZhtL8-Q9LaQz-xszGvF-5Snrk7-XXj8Zo-2kTdpQW-oJNALx-23ujGva-zdbLK7-drUB8o-oJPhuP-p2ioZZ-pAmHWY-6cTe7g-G4hs91-23Vyuc-GDA3y7">https://www.flickr.com/photos/38409567@N07/49748326211/in/photolist-2iN6bbg-2k55VKF-ynKeQG-2k47HeR-2cKyEDR-q53CKq-2jYYMqS-298VYBc-2kPHaaM-4NmPKu-2iEMPjK-2kPMbZE-2kdzaUZ-5MExQj-deqvR2-63ubu6-24hz7Gk-4ZZAco-Q1GS07-2jL5s2s-bB21mU-2c7r6w8-Pvbb4N-22yemc4-4DGQ9C-2kE3jYp-SDNQKx-2jmCuJA-51Wf9j-oPvmLE-EKfzs-zvPs5r-2i8pjoh-ZhtL8-Q9LaQz-xszGvF-5Snrk7-XXj8Zo-2kTdpQW-oJNALx-23ujGva-zdbLK7-drUB8o-oJPhuP-p2ioZZ-pAmHWY-6cTe7g-G4hs91-23Vyuc-GDA3y7</a>	CC BY 2.0
35	Fig 14D, p 57	Many mink crowded in cage, several with cannibal wounds	Nettverk for dyrs frihet	<a href="https://search.creativecommons.org/photos/e34563f0-34da-4d2b-b1e3-3484d7fa2e59">https://search.creativecommons.org/photos/e34563f0-34da-4d2b-b1e3-3484d7fa2e59</a>	CC BY-NC-SA 2.0
36	Fig 14D, p 57	Mink biting pen mate	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/36487141@N02/8119885319">https://www.flickr.com/photos/36487141@N02/8119885319</a>	CC BY-NC-SA 2.0
37	Fig 14D, p 57	White mink no ear (cannibalism)	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/36487141@N02/3365927100">https://www.flickr.com/photos/36487141@N02/3365927100</a>	CC BY-NC-SA 2.0
38	Fig 14D, p 57	Black mink chewed head (cannibalism)	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/36487141@N02/3844472665">https://www.flickr.com/photos/36487141@N02/3844472665</a>	CC BY-NC-SA 2.0

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39	Fig 14D, p 57	Mink tail biting	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/36487141@No2/8119896707">https://www.flickr.com/photos/36487141@No2/8119896707</a>	CC BY-NC-SA 2.0
40	Fig 14D, p 57	Mink bar biting	Nettverk for dyrs frihet	<a href="https://www.flickr.com/photos/dyrsfrihet/3364976345/in/photostream/">https://www.flickr.com/photos/dyrsfrihet/3364976345/in/photostream/</a>	CC BY-NC-SA 2.0
41	Fig 14E, p 58	Isolated mink on ice	Paul Hurtado	<a href="https://www.flickr.com/photos/33323109@No3/16015207249">https://www.flickr.com/photos/33323109@No3/16015207249</a>	CC BY-SA 2.0
42	Fig 14E, p 58	Roaming running wild mink	Ted Goldring	<a href="https://www.flickr.com/photos/88821538@No0/199547389">https://www.flickr.com/photos/88821538@No0/199547389</a>	CC BY 2.0
43	Fig 14E, p 58	Swimming mink	Tom Brandt	<a href="https://www.flickr.com/photos/12567713@No0/561118201">https://www.flickr.com/photos/12567713@No0/561118201</a>	CC BY 2.0
44	Fig 14E, p 58	Mink in cage	dyrevern	<a href="https://www.flickr.com/photos/dyrevern/47255809612/in/photolist-2eZQnQ9-29WFrFd-6562MW-dXqCYC-22Rrr2c-5svPYr-5urt82-PGsZX-RtHypy-nYbks-223A3yN-i74Aoq-i752ZV-Tp6wSo-hLjeQv-i754pP-i74kBx-i74woU-i74nyi-i74JWN-i74Huu-9UHDwZ-7svhif-32Sppd-moZUWj-i75byZ-i74EeJ-5DjFQB-2jkBjhn-24VLNB6-7sziuv-i74EEb-dXraP9-szvs5A-i75g3t-5y38Fq-7NcFkW-acCBZF-RLXTWX-otDXg8-5DjFNg-2Uscji-2ero6Fm-RLXUU8-49RJVc-dXjYqn-8ciiqp-GHqAR-2jp7dfW-2dPNC2E">https://www.flickr.com/photos/dyrevern/47255809612/in/photolist-2eZQnQ9-29WFrFd-6562MW-dXqCYC-22Rrr2c-5svPYr-5urt82-PGsZX-RtHypy-nYbks-223A3yN-i74Aoq-i752ZV-Tp6wSo-hLjeQv-i754pP-i74kBx-i74woU-i74nyi-i74JWN-i74Huu-9UHDwZ-7svhif-32Sppd-moZUWj-i75byZ-i74EeJ-5DjFQB-2jkBjhn-24VLNB6-7sziuv-i74EEb-dXraP9-szvs5A-i75g3t-5y38Fq-7NcFkW-acCBZF-RLXTWX-otDXg8-5DjFNg-2Uscji-2ero6Fm-RLXUU8-49RJVc-dXjYqn-8ciiqp-GHqAR-2jp7dfW-2dPNC2E</a>	CC BY-NC-ND 2.0
45	Fig 14E, p 58	Multiple mink in pen	CAFT	<a href="https://www.caft.org.uk/index.html">https://www.caft.org.uk/index.html</a>	Permission granted to use photo 6.8.12.
46	Box 6, p 64	Figure 1, Pagh et al 2021.	Sussie Pagh	<a href="https://pubmed.ncbi.nlm.nih.gov/33445630/">https://pubmed.ncbi.nlm.nih.gov/33445630/</a>	Creative Commons



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