Detection of new SARS-CoV-2 variants related to mink

12 November 2020

Summary

Since April 2020, when the first SARS-CoV-2 infection was reported in the Netherlands in a mink and subsequently in a mink farm worker, it has been established that human-to-mink and mink-to-human transmission can occur [1]. Since then, infections in mink have been reported in Denmark, Italy, Spain, Sweden and the United States [2].

On 5 November 2020, Denmark reported 214 human COVID-19 cases infected with SARS-CoV-2 virus variants related to mink, as well as infected mink at more than 200 mink farms. Most human and animal cases reported since June 2020 have been in the North Jutland Region. The SARS-CoV-2 variants detected in these cases were part of at least five closely-related clusters; each cluster was characterised by a specific mink-related variant, identified in humans and animals from infected mink farms. Denmark has implemented robust response measures to control the outbreaks in mink and decrease the spill-over between the human and the animal reservoir.

One of the clusters (Cluster 5), which was reported as circulating in August and September 2020, is related to a variant with four genetic changes, three substitutions and one deletion, in the spike (S) protein. Since the S protein contains the receptor-binding domain, and is a major target for immune response, such mutations could, in theory, have implications for viral fitness (ability to infect humans and animals), transmissibility, and antigenicity. As a consequence, the evolution of viruses with increasing changes in functional domains of the S 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. Investigations and studies are ongoing to clarify the extent of these possible implications.

What is the risk to human health posed by SARS-CoV-2 mink related variants?

Transmissibility

Current evidence available from Denmark and the Netherlands on SARS-CoV-2 variants related to mink indicates that these variants are able to circulate rapidly in mink farms and the human communities close to the farms, however, they do not appear to be more transmissible than other circulating SARS-CoV-2 variants. Thus, the probability of infection with mink-related variant strains is assessed as low for the general population, moderate for populations in areas with a high concentration of mink farms and very high for individuals with occupational exposure.

Severity

Patients reported to be infected with mink-related variants, including the Cluster 5 variant in Denmark, do not appear to have more severe clinical symptoms than those infected with non-mink-related variants. Therefore the current impact of COVID-19 on disease severity in patients infected with any mink-related variant appears to be similar to those infected with non-mink-related variants. This impact was previously assessed as low for the general population and very high for individuals with risk factors for severe COVID-19 disease, such as the elderly.

Suggested citation: European Centre for Disease Prevention and Control. Detection of new SARS-CoV-2 variants related to mink – 12 November 2020. ECDC: Stockholm; 2020.

Immunity, reinfection, vaccination and treatment

Of all mink-related variants analysed so far, only the Cluster 5 variant has raised specific concern due to its effect on antigenicity. Further investigations are needed to assess whether this may have any impact on i) the risk of reinfection, ii) reduced vaccine efficacy or iii) reduced benefit of treatment with plasma from convalescent patients or with monoclonal antibodies. It should be noted that continued transmission of SARS-CoV-2 in mink farms may eventually give rise to other variants of concern.

Cross-border spread

The cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through humans has not been observed so far, but there is no indication that the potential for cross-border spread is different to that for other SARS-CoV-2 variants. Genetic adaptation in mink populations could give rise to a selective advantage in regions with mink farming activity. The mutation Y453F, defining mink-related variants, has also been detected outside of Europe, indicating the potential for circulation of such strains. In the past few months, community transmission has occurred in Denmark and, to some extent, in the Netherlands, which could lead to cross-border spread.

The cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through animals and animal products appears very low.

Conclusion

Based on the information currently available on transmissibility, severity, immunity and cross-border spread, the overall level of risk to human health posed by SARS-CoV-2 mink-related variants can be determined as:

- low for the general population and moderate for medically-vulnerable individuals, which is no different to other SARS-CoV-2 strains (not related to mink);
- low for the general population in areas with a high concentration of mink farms and moderate-to-high for medically-vulnerable individuals living in the same areas;
- moderate for non-medically vulnerable individuals with occupational exposure and very high for medically-vulnerable individuals with occupational exposure.

If the concerns raised in relation to immunity, reinfection, vaccination and treatment are confirmed, the risk assessment will be immediately reviewed to re-assess the overall level of risk to human health and the potential implications for COVID-19 diagnosis, treatment and vaccine development. This also applies to any further mink-related variants with mutations in the S protein that may arise and spread in the EU/EEA and the UK.

Options for response

To decrease the risk posed to public health, national authorities should consider implementing measures aimed at mink farms, mink farm workers and communities in contact with mink farms along the lines below.

Human testing, sequencing and characterisation of antigenic properties and virus infectivity – national authorities should implement a systematic approach to testing and sequencing, particularly in mink farm workers and nearby communities. Outbreak investigations, comprehensive testing of workers and contact tracing, isolation and quarantine should be immediately initiated if a human case is identified related to a mink farm. Mutations of concern should be reported and assessments of antigenicity and viral infectivity should be developed.

Infection prevention and control measures for mink farm workers and visitors – the number of people in contact with mink and mink farms should be limited and farm workers with COVID-19-compatible symptoms should not have access to the farms. Appropriate technical and organisational measures should be taken to ensure the health and safety of workers in the workplace. Workers should be informed, trained and provided with appropriate personal protective equipment , including respiratory and eye protection. The possibility of language barriers for seasonal workers at mink farms needs to be considered when implementing hygiene and prevention measures on the farms.

Animal testing and prevention of spread from animals – monitoring and surveillance of mink farms (repetitive surveys and/or testing of dead mink on weekly basis) should be undertaken for as long as SARS-CoV-2 exposure from humans to mink cannot be excluded. It is recommended that isolated SARS-CoV-2 strains be genotyped systematically according to validated protocols and genome sequences from all infected animals, in particular mink, should be shared. This will enable the rapid identification of possible clusters and related variants. Culling of mink and destruction of raw pelts from infected farms should be considered in accordance with appropriate biosecurity measures.

Development of One Health preparedness and response strategies – enhanced coordination between the agricultural, animal health, and human health (including occupational health and safety) sectors is essential for a timely and effective response. It is also important to increase public awareness of mink-related SARS-CoV-2 prevention and control strategies specifically targeting mink producers, mink farm workers, veterinarians and veterinary staff working with mink farms and partners in the fur industry.

Event background

As of 5 November 2020, Denmark had reported 214 human COVID-19 cases infected with SARS-CoV-2 related to mink (all carrying the mutation Y453F in the spike (S) protein, referred to as mink-related variants). These cases are part of an ongoing spread with both zoonotic and anthroponotic transmission. The 214 cases represent 4.2% of the 5 102 human samples sequenced in Denmark from week 24 (8–14 June) to week 42 (12–18 October) 2020, when many mink farm outbreaks in the north-west of the country were reported. The 5 102 sequenced strains accounted for 13% of the total number of 37 967 cases reported in Denmark during the period in question.

Of the 214 human cases infected with mink-related virus variants, 12 human cases were infected with strains showing four genetic changes in the S protein; three substitutions and one deletion. This cluster is referred to in the Danish risk assessment as Cluster 5 [1]. The 12 human cases were reported in the North Jutland Region in August and September 2020 and not all of them had a direct link to a mink farm.

Statens Serum Institut (SSI) in Denmark has developed and validated a wild-type virus microneutralisation antibody assay, to investigate possible antigenic changes related to the genomic changes identified in the S protein. Preliminary results, using a panel of convalescent sera from humans (n=9), infected with common circulating SARS-CoV-2 strains during spring 2020 with low, medium and high neutralising antibody titers, exhibited an average of 3.58-fold (range 0–13.5) reduction [3]. However, only three of the strains exhibited a 4-fold reduction when tested with the virus isolate from a patient with the Cluster 5 virus variant, compared to the unmutated common wild-type SARS-CoV-2 strain. A 4-fold reduction is commonly required for an assessment of significant antigenic changes in new influenza strains [4], however as yet there is no similar agreement for SARS-CoV-2 strains since no set of reference sera has been established. These findings indicate that there could be a potential impact on antibody-mediated immunity provided by SARS-CoV-2 infection or vaccines. It should be noted that these findings are preliminary and have to be confirmed before any conclusions can be drawn. Further studies, using more virus isolates from humans infected by mink-related strains with different genomic changes, have been initiated and confirmation from other investigators is being sought in Denmark and internationally. The Danish risk assessment stresses that if these new SARS-CoV-2 variants with lower susceptibility to neutralising antibodies spread widely in the population it might have an impact on the level of vaccine effectiveness for the vaccines currently under development. Furthermore, the establishment of a virus reservoir among mink may give rise to problematic virus variants in the future.

Mink-related SARS-CoV-2 variants in Denmark and the Netherlands

The 214 mink-related cases reported by Denmark all involve strains with the S protein mutation Y453F. The mutation Y453F has been observed in several clusters related to mink farms in the Netherlands [5]. The strains from the Netherlands and Denmark are not closely related and fall into different genetic clades, which excludes a direct link between farms in the two countries. From the sequence data available from Denmark so far it is not possible to determine the extent to which mink-to-human transmission is currently contributing to transmission chains. Some of the strains from mink in the Netherlands lack Y453F, which demonstrates that it is not a prerequisite for infecting mink, but probably a selected mutation in the mink population [6,7]. Variants with Y453F, unrelated to the Danish and Dutch variants, have also been reported sporadically from other countries (the Russian Federation, South Africa, Switzerland, and the United States) in the GISAID EpiCoV sequence database [6]. These variants have come from human cases without a known link to mink farms, which suggests that the strain may not always be related to mink, unless there was undetected mink-to-human transmission.

About half of the mink-related strains reported by Denmark additionally carry a deletion of two amino acids (69-70) in the S protein. This mutation is not present in any of the mink strains from the Netherlands but has been widely reported in unrelated human cases without Y453F in the GISAID EpiCoV database (from Australia, Canada, Côte d'Ivoire, France, Germany, Malaysia, New Zealand, Norway, Sweden, and the United Kingdom). The Cluster 5 variant strains carry two additional mutations in the S protein (I692V, M1229I) for a total of four S protein mutations, one of which (Y453F) is located in the receptor binding domain (RBD).

The Danish health authorities have not observed changes in the human-to-human transmissibility of the virus or severity of disease for any of the mink-related variants in Denmark. The Cluster 5 variant was last observed in Denmark on 14 September 2020, which may suggest that it is no longer circulating. However, viruses with the S protein Y453F mutation have become increasingly common and are now causing approximately 40% of the COVID-19 cases in the North Jutland Region. In the Netherlands, the viruses with the Y453F mutation related to mink farms did not continue to circulate.

The sequences of the mink-related viruses from Denmark and the Netherlands have been deposited with GISAID EpiCoV by the national sequencing laboratories [6]. These include representative sequences from Denmark with Y453F only (EPI_ISL_618040), with additional del 69-70 (EPI_ISL_616269) and from Cluster 5 (EPI_ISL_616695). Denmark is also expanding sequencing capacity for human and mink SARS-CoV-2 infections.

Outbreaks of SARS-CoV-2 infections in mink farms

According to the World Organisation for Animal Health (OIE), SARS-CoV-2 infections in animals are notifiable [8,9]. As of 6 November 2020, six countries had reported SARS-CoV-2 infections in farmed mink to OIE: Denmark, Italy, the Netherlands, Spain, Sweden and the United States [2]. Outbreaks affecting mink-farms have been observed in large numbers due to the apparent high susceptibility of mink to SARS-CoV-2 infection, coupled with the highly intensive characteristics of mink farming [10,11].

Denmark is one of the largest mink fur producers in the world. On 17 June 2020, Danish authorities reported the first identification of SARS-CoV-2 in mink at a farm in the North Jutland Region [1,12]. Since early-August 2020, large SARS-CoV-2 infection outbreaks have been reported in mink farms in Denmark. Despite intensive efforts to contain the outbreaks, as of 8 November 2020 the virus had been detected in 229 (20%) of the 1 140 mink farms in the country [13]. Affected farms are located in northern, central and western Jutland regions. In the majority of the infected farms, the PCR and sero-prevalence in mink were close to 100% by the time the outbreak was detected. Links between human cases and mink outbreaks were found, although it was often not possible to determine whether mink or humans were infected first. To contain the spread of mink farm outbreaks, a range of measures have been implemented at various stages during the epidemic. Measures include the culling of infected mink, enhanced surveillance of the local human population, including population-wide mass RT-PCR testing in the North Jutland Region, movement restrictions in the affected areas, limited access to the farms (for employees only), and application of strict hygiene routines - e.g. hand washing and changing clothes before and after entering farms. Local restrictions, including restricted movement of people between municipalities, have been implemented for the period 9 November 2020 to 3 December 2020 in the North Jutland Region [14,15]. Since 4 November 2020, the government of Denmark has been discussing a cull of all mink in the country [16].

The Netherlands reported SARS-CoV-2 infections at 69 mink farms in three regions during the period 23 April to 5 November 2020 [17]. At the time of the first identification, a mink-related variant was reported in a farm employee, suggesting the first possible case of animal-to-human SARS-CoV-2 transmission [5]. Since 20 May 2020, mink farmers, veterinarians and laboratories have been obliged to report clinical signs and SARS-CoV-2 infections in mink to the Netherlands Food and Consumer Product Safety Authority (NVWA). In addition, an early warning system is in place whereby animals are tested and results reported every week. Since 28 May 2020, national measures have been in place for all mink farms. On 3 June 2020, the national authorities decided to cull mink at the affected farms. On 28 August 2020, it was announced that the effective date of a ban on mink farming in the Netherlands will be brought forward from 1 January 2024 to early 2021 [18]. Following the first SARS-CoV-2 infection outbreaks at mink farms in the Netherlands, an epidemiological investigation concluded that the most likely explanation for the infection at the mink farms is the introduction of the virus by humans and subsequent transmission among the mink.

Mink are housed in adjoining cages made of wire netting, allowing free airflow and contact between animals in adjacent cages, which explains the rapid animal-to-animal transmission. Furthermore, the presence of viral RNA in inhalable dust collected from inside the farms indicates the possibility of workers having been exposed to the virus in mink excretions. Following outbreaks of SARS-CoV-2 infection at mink farms in the Netherlands during 2020, the points below should be borne in mind.

- Mink-to-mink transmission is very efficient.

- No link has been identified between infected farms.

- A proportion of farm animals had clinical symptoms suggestive of acute respiratory illness for about four weeks, but some animals were still RT-PCR–positive for SARS-CoV-2 in throat swabs after clinical symptoms had disappeared. This may vary, as seen recently in Danish outbreaks, where clinical symptoms were observed for shorter periods.

- The high diversity in the sequences from some mink farms can probably be explained by the existence of many generations of infected animals before an increase in mortality was observed.

- The current estimates are that the substitution rate of SARS-CoV-2 is one mutation per two weeks. There was also a relatively high sequence diversity observed in farms, which still tested negative one week prior to the outbreak, implying that the virus evolves more quickly in the mink population. This can indicate that the virus might replicate more efficiently in mink or that it may have acquired mutations which make it more virulent in mink [5].

Italy reported one mink (weakly) positive for SARS-CoV-2 at a farm in the Lombardy region on 10 August 2020. No lesions were found in this mink. The detection came after the identification of a case of COVID-19 in a worker from the farm. In response, around 1 500 mink were tested and no further cases were detected. Surveillance activities are ongoing at mink farms [19].

Spain reported SARS-CoV-2 infections at a mink farm in the Aragon region. On 21 May 2020, seven asymptomatic infections were reported among workers at a mink farm in Aragon, according to media quoting the Spanish health authorities [20]. Hygiene and biosecurity measures were put in place and the movements restricted in relation to the farm. No clinical symptoms were observed among the animals at the farm. On 22 June 2020, one animal tested positive by RT-PCR for SARS-CoV-2. On 7 July 2020, 78 of the 90 animals tested were found positive by RT-

PCR. The Government of the Autonomous Community of Aragon decided to proceed with the safe disposal of the carcasses and other potentially infected materials, after which the facilities were cleaned and disinfected [21].

As of 6 November 2020, Sweden had reported ten SARS-CoV-2-positive mink at farms in Blekinge county, where the first detection in one mink occurred on 16 October 2020. Several mink that had been found dead also tested positive. Sequences from two mink and two human cases have been reported without any S protein mutations. Surveillance at the 40 mink farms in Sweden is ongoing. There are no plans to cull at present. However, movement restrictions are in place and strict biosecurity measures have been imposed on all mink farms in Sweden [22-24].

As of 30 October 2020, 11 outbreaks in commercial mink farms have been reported in three states of the United States. These outbreaks occurred between 26 July and 29 September 2020. Several people that were in contact with mink from these farms also tested positive for SARS-CoV-2. In total, 12 231 mink died as a result of contracting the virus. In response to these outbreaks, state officials quarantined the premises and worked with One Health partners to dispose of deceased mink, and are continuing to monitor the situation. No mink were culled as a result.

Disease and virus background

For information on the latest scientific evidence relating to COVID-19, please visit ECDC's website:
https://www.ecdc.europa.eu/en/2019-ncov-background-disease

Mink farming and susceptibility of mink to respiratory viruses and viral adaptation in infected mink

SARS-CoV-2 can infect several species of domesticated animals, the most highly susceptible are felines (cats, tigers, lions), ferrets, mink, Golden Syrian hamsters, Egyptian fruit bats (*Rousettus aegyptiacus*) and Macaques (*Macaca fascicularis* and *Macaca mulatta*) [26-28]. Susceptibility of several species within the family Mustelidae (such as mink and ferret) to respiratory viruses (e.g. influenza) has been demonstrated in natural and experimental conditions. Cross-species transmission, particularly of influenza viruses, has been reported from companion animals and captive wild animals. In Danish mink farms, the median daily mortality observed in mink during the peak of SARS-CoV-2 epidemic has been 0.14% (5th-95th percentiles: 0–0.74%), compared to a baseline mortality close to zero (e.g. 1-4 animals /month per farm with an average size of 10 000 mink per farm). Therefore, in mink farms any increased mortality is easily detected, although the virus may have already entered the farm some time before.

The introduction of species-specific adaptation mutations and reassortment events of influenza virus in infected mink populations have been described. This underlines the importance of the species for the acquisition of mutations and generation of antigenically diverse viruses, mainly respiratory, which spread quickly between mink at the densely-populated farms. Ferrets are the standard model for assessing the potential of airborne transmission of influenza viruses, particularly those viruses with pandemic potential, and these animals have been used as a model to test transmissibility of SARS-CoV-2 [29,30]. Ferrets and mink belong to the same family of animals, but are not directly or closely related [31]. The American mink (*Neovison vison*) is mainly used to produce fur and large outbreaks of respiratory viruses at farms have been described. However, such infections have also been observed in free living European mink (*Mustela lutreola*). In recent decades, mink escaping or being released from breeding farms in Europe has led to the establishment of a feral population of American mink in several European countries [32].

At mink farms, the whole production cycle (including breeding, lactation, weaning, growing and finally r pelting) occurs in a closed system on the same farm over a period of one year. The close proximity of mink housing may facilitate efficient animal-to-animal transmission of diseases. Three main breeding periods can be defined: from pelting to mating, from mating to separation, from separation to pelting. Conditioning and breeding take place in the period December–March, followed by whelping and weaning (April–June), growth and furring (July–October) and grading and slaughter (November–December). The pelting season begins in November/December. During the pelting process, the pelt is prepared in such a way that it can be kept for up to a year without being dressed. The pelts are placed on drying boards to maintain their shape during the drying process. The rest of the carcass is recycled for use in the production of bio-diesel, fertilisers, among other products.

Europe is the global leader in fur production, with more than 27 million mink pelts produced annually (2019) at more than 2 750 mink farms, 1 100 of which are in Denmark [33] (Annex 1, Figure 1, 2 and 3).

Mink farms often employ seasonal workers who come from abroad during the periods of mating, whelping, vaccination and pelting for various lengths of time during the year [25].

SARS-CoV-2 spike protein variants and their impact on viral infectivity and antigenicity

SARS-CoV-2 has accumulated mutations since its emergence in the human population in 2019. On average a genome from a virus collected in October 2020 had around 20 accumulated mutations compared to the first strain sequenced in January 2020 (Wuhan-Hu-1) [34,35]. Most of these mutations are expected to be neutral or detrimental to the virus fitness in the human population, while a few may provide some selective advantage, such as increased infectivity [36,37]. When a virus switches host species, an increased mutation rate can be observed due to the virus adapting to its new host [38]. Mutations in the structural proteins of the virus, altering the antigenic properties of the strain, can lead to reduced effectiveness of the immune response if the immunity was acquired through infection by a strain, or a vaccine derived from a strain, without these mutations [39].

Thanks to laboratories sharing genomic data in databases, such as GISAID EpiCoV [6] and the COVID-19 data portal [40], and visualisations provided by free online platforms [35,41,42], the evolution of SARS-CoV-2 can be followed.

For SARS-CoV-2, the most important structural protein in this context is the S protein as it binds to the ACE-2 receptor during the entry of the virus particle into human cells; the part of the protein that directly binds to the receptor is called the receptor binding domain (RBD) [43,44].The RBD has been shown to be less conserved than the rest of the S protein in circulating SARS-CoV-2 [45].

It is not possible to predict accurately what effect individual structural protein mutations will have on antigenic properties from the virus sequence data alone. The location of mutations in genes coding for the structural proteins can provide an indication [46], but experimental evidence is needed to provide a better estimate of the effect on the immune response. A common method used to assess antigenic properties is neutralisation assays, where the mutated virus is grown in the laboratory in the presence of serum from humans or animals that have been infected by a strain, or vaccinated with a vaccine derived from a strain without the mutations [47].

The ability of SARS-CoV-2 to infect an animal depends on several factors that are not fully understood, including compatibility between the S protein of the virus and the host receptor ACE-2. Mink can be infected by SARS-CoV-2 and they can also transmit the virus to humans [48]. It is rare that a novel variant becomes successful and gives rise to a new genetic clade that can spread globally. When this happens, it can be due to spurious founder effects and/or selective advantages [49]. If the spread among mink is not controlled and there is recurrent spill-over into the human population, variants that provide a selective advantage in mink populations could become widespread in humans, even without any selective advantage in the human population.

During the summer and autumn of 2020, S protein mutations unrelated to mink have emerged and become widespread in the EU/EEA and the UK. These include amino acid substitutions A222V and S477N, which are increasing in proportion, although no selective advantages or changes in antigenic properties have been demonstrated [50], and N439K, for which reduced neutralisation effect by convalescent sera has been demonstrated [45].

The impact of mutations in the SARS-CoV-2 S protein on viral infectivity and antigenicity have been assessed for eighty natural variants and twenty-six glycosylation spike variant strains using a pseudovirus assay [51]. Most variants observed with amino acid change in the receptor binding domain were less infectious, while some variants - including A475V, L452R, V483A and F490L - were resistant to some neutralising antibodies.

Virus mutations can affect the sensitivity of diagnostic assays that detect nucleic acid, antigen or antibodies. None of the mink-related variants reported by Denmark [52] are known to cause any issues with existing RT-PCR assays as none of the mutations defining the mink-related clusters are located within the amplicons of RT-PCR assays recommended by WHO, and such assays generally do not target the S gene. The variants could potentially affect antigen and antibody detection assays and further investigations are needed to assess this.

Development of immunity including neutralising antibodies to SARS-CoV-2 viruses in humans

In most infected individuals, antibody responses to SARS-CoV-2 can be detected 10–15 days after onset of COVID-19 symptoms.

Sequential serum samples collected up to 94 days after onset of symptoms in laboratory-confirmed human cases show that antibodies, including IgM, IgA, IgG and neutralising antibodies, develop in more than 95% of cases [53]. A wide range of SARS-CoV-2 neutralising antibody titres have been reported after infection and these vary depending on the length of time from infection and the severity of disease [54-56]. Neutralising antibodies can be assessed using either wild-type SARS-CoV-2 virus or a pseudotype neutralisation assay, and a correlation between the two has been shown [57]. A surrogate neutralisation assay using soluble RBD which can be performed at biosafety level 2 has also been described [58]. In the study mentioned above using a pseudotype neutralisation assay, the kinetics of the neutralising antibody responses were characterized over time and an initial peak was observed, which subsequently declined. The height of this peak at 3–4 weeks post onset of symptoms, with titres ranging from 98–32 000, and the subsequent rate of decline over time to levels still above or at base-level with no neutralising antibodies, was shown to be dependent upon disease severity.

The neutralising antibody titre required for protection from reinfection and/or a new symptomatic disease in humans is not yet understood. In animal challenge models it has been shown that selected highly-potent neutralising monoclonal antibodies isolated from SARS-CoV-2 infected individuals can protect in a dose-dependent manner [59-61].

First results from immunogenicity, assessed in phase 1/2 clinical trials testing vaccine candidates that may possibly become available in the EU, have shown peak median neutralising antibodies ranging from 100 to 3 900 titres for various vaccine candidate constructs [62-65]. However, it is acknowledged that different assays and formats were used, making any direct comparison problematic [66].

Further characterisation of the correlates of protection and longevity of vaccine-induced protection is needed, including the role of T-cell-mediated immunity. For assessment of B- and T-cell immunity, further standardisation is necessary to allow for comparability. To support these efforts, the Coalition for Epidemic Preparedness Innovations (CEPI) recently set up a centralised laboratory network to standardise methods for assessment of COVID-19 vaccine candidates [67].

Risk assessment

This assessment is based on information available to ECDC at the time of publication and, unless otherwise stated, the assessment of risk refers to the risk that existed at the time of writing. It follows the ECDC rapid risk assessment methodology, with relevant adaptations [68]. The overall risk is determined by a combination of the probability of an event occurring and its consequences (impact) for individuals or the population [68].

What is the risk to human health posed by SARS-CoV-2 variants related to mink?

Transmissibility

Human cases of SARS-CoV-2 infection originating from variants related to mink have been identified in Denmark and the Netherlands. In Denmark, viruses from around 13% of human cases have been sequenced so far. Of these viruses, 214 have been identified as mink-related variants since the first outbreak at a mink farm was reported in June 2020 [1]. Some of these cases have no known link to mink farms. COVID-19 incidence of human cases in the North Jutland Region is higher than in the neighbouring regions. In this region, from June to October 2020, around 40% of cases where the virus was sequenced were caused by a mink-related variant. However, the sampling strategy applied is not the same as in other regions and therefore the incidence cannot be directly compared [69]. The Cluster 5 variant has not been identified since September. Nevertheless, undetected circulation cannot be ruled out, as not all cases are detected and not all viruses sequenced.

In the Netherlands, at least 66 of 97 farm employees tested were positive for SARS-CoV-2 and at least 47 human cases infected with mink-related variants were confirmed by whole genome sequencing. However, only limited human transmission has been reported outside of mink farms since the first mink farm outbreak was identified in April 2020.

Different patterns of transmission after spill-over events in a variety of settings could be due to prevention and control measures at farm and/or country level, surveillance and sequencing capacities, or the inherent transmissibility of the strain.

The information available to date from outbreaks of mink-related strains in Denmark and the Netherlands does not demonstrate increased transmissibility of mink-related variants compared to other variants of SARS-CoV-2, even though uncertainties remain.

On the basis of the evidence available, the probability of infection with mink-related variant strains is assessed as low for the general population, moderate for the populations in areas with a high concentration of mink farms and very high for individuals with occupational exposure.

Severity

Patients reported to be infected with mink-related variants, including Cluster 5 variant in Denmark, do not appear to have more severe clinical symptoms than those infected with non-mink related variants, either in Denmark, or in the Netherlands. However, there is still a high level of uncertainty due to the small number of cases reported so far.

On the basis of the information available, the current impact of COVID-19 on disease severity in patients infected with mink-related variants appears to be similar to that for patients infected with non-mink variants. This has previously been assessed by ECDC [70] as low for the general population and very high for medically-vulnerable groups (individuals with risk factors for severe COVID-19 disease, such as the elderly) [71]).

Immunity, re-infection, diagnostic tests, vaccination and treatment

Of all the mink-related variants analysed so far, only the Cluster 5 variant has raised specific concern due to its effect on antigenicity and this requires specific assessment. In preliminary studies, this variant showed reduced sensitivity to neutralising antibodies from COVID-19 patients during the spring of 2020. Antibodies generated by

natural infection with other variants and the antibodies generated by vaccines may potentially exhibit reduced neutralisation in individuals infected with this variant. T-cell mediated immune responses have not yet been investigated for this variant. It should be noted that these findings are preliminary and need to be confirmed before any conclusions can be drawn. Further investigations are needed to assess the impact on i) the risk of reinfection, ii) reduced vaccine efficacy or iii) reduced benefit from treatment with plasma from convalescent patients or with monoclonal antibodies. If any of these concerns are confirmed, given the extent of spread of the mink-related strains in the human population, the current assessment will be immediately reviewed to increase the overall level of risk to human health.

If SARS-CoV-2 transmission among mink affects a very large number of animals and/or is sustained over long periods of time, there is a risk that variants with significantly different antigenic properties or variants causing increased severity of disease could eventually emerge. The likelihood of this risk and the consequences are unclear, but such a scenario should be taken into consideration.

The sensitivities of diagnostic RT-PCR assays are not affected by the Cluster 5 variant or other Danish mink-related S protein variants as RT-PCR assays do not target the spike gene. The variants could potentially have an effect on the sensitivities of antigen and antibody detection assays, including rapid antigen tests (RATs), although any effect will probably be small. Further investigations are needed to determine such effects.

Cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through humans

It is rare that a novel variant becomes successful and gives rise to a new genetic clade that can spread globally, but adaptation to transmission in mink populations could establish a selective advantage in regions with mink farming activity.

The mutation Y453F, found both in Denmark and the Netherlands and linked to mink, which is believed to confer a selective advantage in mink-to-mink transmission, has also been detected sporadically in Russian, South African, Swiss and US sequences with no link to the variants found in Denmark or the Netherlands. This could be an indication that this mutation can also arise in humans, or that there is undetected sporadic mink-to-human transmission of SARS-CoV-2 in these countries. It is also possible that low level circulation of these strains is already occurring unnoticed in some places due to the lack of comprehensive sequencing information for all confirmed human cases. The geographically uneven sequencing coverage and delay between sampling and upload of sequence data to international databases is delaying the overall availability of information and limiting the assessment of geographical spread of the new variants beyond affected areas.

Workers employed at mink farms which are not fully compliant with hygiene measures could also introduce the mink-related variants to the community in the vicinity of the farm, new areas or other countries when travelling or returning home while infected. Such events could contribute to the cross-border spread of new variants.

In summary, the probability of cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through humans appears to be high, in the same way as it is for other SARS-CoV-2 strains.

Increased surveillance, involving collaboration and communication between animal and public health authorities, testing and sequencing of samples from mink farm workers and populations living near mink farms may help prevent the introduction of SARS-CoV-2 into mink farms and identify cases of SARS-CoV-2 infection early.

Response measures currently implemented to control the COVID-19 pandemic have reduced population movement as well as travel and may help to lower the possibility of new variants spreading rapidly to other countries. With the increasing incidence of COVID-19, it is becoming very challenging to detect and characterise specific clusters or outbreaks. However, increased testing, sequencing, contact tracing, isolation of cases, and the general strengthening of public health measures currently being implemented in many countries may help identify clusters of cases due to newly emerging mink-related variants early on to prevent spread in the community.

Cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through animals and animal products

It is also important to consider that cross-border transmission of SARS-CoV-2 variants is possible through the trade of infected animals or animal products. The possible pathways for transboundary circulation of mutated SARS-CoV-2 linked to movement of mink or mink products are discussed below.

Transport of live mink

Around 1% of the annual production (mainly breeding animals) are transported alive [72]. Transport of infected mink not displaying clinical symptoms and without prior testing can contribute to the spread of infection between mink farms. Given the seasonality of mink production, live mink are mainly transported during the period December-March. Thus, the many outbreaks occurring from April to November 2020 were probably not caused by mink transport. Given the events reported in 2020 and the awareness of the risk of SARS COV-2 in mink, along with the fact that surveillance and a ban on movement is now in place in most Member States, putting a stop to the transport of live mink will reduce the probability of transboundary spread of SARS-CoV-2. For example, the Netherlands will end mink production by the end of 2020. Denmark, the largest mink fur producer in the world, has introduced robust response measures to limit the movement of mink, thus drastically reducing the transport of live mink. As a consequence, the risk of transboundary spread of SARS-CoV-2 out of Denmark will become negligible. Transport of pet mink is extremely rare as mink are usually not kept as pet.

Accidental escape from farms

Release of farmed mink into the wild has been reported, either as a result of accidental escape or intentional release by animal welfare activists. Denmark adopted new containment measures in 1999 which reduced the number of farm-originated mink in the wild (from a hunting bag of 8 000 mink in 2000 to 2 000 mink in 2016 and 1 638 in 2018) [73,74]. A variety of containment measures adopted across Europe have reduced the risk of accidental escapes. However, deliberate releases still occur occasionally in Europe as an act of protest against mink farming by animal welfare activists (in Denmark several thousand per year) [74]. In Spain, around 200–300 feral mink (farmed mink escaped into the wild) are caught each year, mainly in the areas of Burgos and Catalonia [75,76]. If infected mink escape into the wild there may be a risk of SARS-CoV-2 spreading to other susceptible wild or domestic species (e.g. cats), although the exposure to humans is limited. The probability of a wild animal being exposed to infected with SARS-CoV-2 from farmed (infected) mink is probably low. Mink farms generally have a perimeter fence and traps within compounds, which are meant to keep wildlife out and prevent mink from escaping. If infection were to occur among wild mink the spread would be limited and transient. The solitary and territorial nature of mink means that widespread transmission would be unlikely. Overall, the probability of cross-border spread of mutated SARS-CoV-2 through the movement of infected mink having escaped or been released from farms is considered very low.

Mink-derived products

In SARS-CoV-2 infected mink farms, mink pelt can be contaminated by the virus through faeces, respiratory droplets and saliva. Based on a study by Riddel et al. (2020)[77], it is probable that SARS-CoV-2 on the pelt of live mink can remain viable for 1–2 weeks. SARS CoV-2 persists on surfaces for up to 28 days, depending on environmental conditions and surface material [77]. Persistence is reduced in hot and dry environments, while only minimal reduction in virus concentration has been observed after 21 days at 4°C and -80°C [78].

After skinning, raw fur pelts are blow-dried for a few hours at room temperature and stored refrigerated or frozen at the farms where the animals are bred. In rare cases, where very small farms have limited pelting capacity, carcasses are transferred to pelting centres where they are stored frozen until they are processed. After drying, pelts are stored at farms for a few days before being transported to auction houses. When mink are pelted, the drying process and the storage period will reduce the virus load on pelts [79], although this may not completely inactivate the virus, which may remain viable on the raw pelts transported to other areas for further processing [78]. Additional contamination of raw pelts by an infected person cannot be excluded.

Processed pelts are considered to be safe, as SARS-CoV-2 is inactivated in the chemical tanning processing [80]. In the tanning process detergents, antibacterial agents, potassium alum and other salts dissolved in water are used. The tanning process lasts 4–5 days during which the leather undergoes washing, fattening and other mechanical operations to improve its quality, often in acidic pH baths. The procedures applied, carried out by trained and protected personnel, the acidity of the baths and the execution times do not favour the survival, proliferation and transmission of bacteria or viruses. The storage, drying and/or tanning process, requiring many washes and the further drying of the product, will ensure that all trace of the virus is removed. Based on these data, processed pelts are not considered a source of SARS-CoV2, and therefore the probability of spread of SARS-CoV-2 variants from processed pelts is considered very low.

Similarly, other products derived from mink carcasses after pelting (mink oil, fertilisers, bio-fuels, etc.) also undergo rendering treatments [81] which inactivate the virus, meaning that there is no probability of mink-related variants being spread.

In summary, the probability of cross-border spread of SARS-CoV-2 variants related to mink in EU/EEA countries and the UK through animals or animal products appears very low, although stronger evidence is needed, to determine whether raw mink pelts from infected mink may represent a source of viable virus when transported to other areas.

Conclusion

Based on the information currently available on transmissibility, severity, immunity and cross-border spread, the overall level of risk to human health posed by SARS-CoV-2-mink-related variants can be stratified as follows:

- low for the general population and moderate for medically-vulnerable individuals, which is the same as for other SARS-CoV-2 strains (not related to mink);
- low for the general population in areas with a high concentration of mink farms and moderate-to-high for medically-vulnerable individuals living in the same areas;
- moderate for non-medically-vulnerable individuals with occupational exposure to mink farms and very high for medically-vulnerable individuals with the same occupational exposure.

It is important to note that if the concerns raised in relation to immunity, reinfection, vaccination and treatment are confirmed, the risk assessment will immediately be reviewed to re-assess the overall level of risk to human health and the potential implications for COVID-19 diagnosis, treatment and vaccine development. This also applies to any further mink-related variants with mutations in the S protein that may arise and spread in the EU/EEA and the UK.

Options for response

The risk control measures set out below should be considered in response to this event.

Human testing, sequencing and characterisation of antigenic properties and virus infectivity

Close collaboration between animal and public health authorities under the One Health approach is crucial for the early detection of SARS-CoV-2 infection outbreaks at mink farms and human cases related to mink farms, to allow timely response and control measures. Information on human and animal cases needs to be shared as quickly as possible to prevent COVID-19 being introduced into mink farms and the SARS-CoV-2 virus circulating undetected. This will also prevent human infection in people exposed to positive cases or farms, and further spread in the community. Information should also be shared with occupational safety and health authorities, to ensure appropriate measures are taken to inform and adequately protect workers at these farms.

Member States should consider a systematic and possibly incremental approach to the proportion of SARS-CoV-2 positive specimens to be sequenced in order to expand the representativeness of the geographical distribution in the population, and to improve the early detection of mutations to better understand the spread. ECDC will continue to support SARS-CoV-2 sequencing for human cases at the request of the Member States.

If a mutation of concern is detected, this should immediately be reported to national and European authorities (through the Early Warning and Response System - EWRS) and the international community. Sharing sequences regularly in open databases and early communication of epidemiological and microbiological investigation results is encouraged in order to improve knowledge of SARS-CoV-2 variants.

Testing and sequencing of suspected SARS-CoV-2 infection cases in mink, farm workers or visitors to mink farms during the incubation period is advised.

Health authorities should consider regularly testing for SARS-CoV-2, irrespective of COVID-19-like symptoms, in farm workers and people with access to premises where mink are kept in order to identify human infections early, prevent introduction into farms and animal populations and avoid further spread in the community/among co-workers. The use of RT-PCR is advised over antigen tests to avoid false negative test results which could increase the risk of community spread. In the event of a positive RT-PCR, sequencing is advised. With a positive detection in a worker, an outbreak investigation should be initiated immediately, and the testing of all workers considered. Exposed workers and visitors should be quarantined as quickly as possible. Appropriate measures also need to be taken to avoid the spread of infection in seasonal workers' accommodation. Workers should be informed and advised, as well as receiving appropriate support to prevent further infections and spread to other countries or geographical areas. Contact tracing should be rapidly implemented and enhanced testing and sequencing of the surrounding population is advised to identify possible circulating mink-related variants.

If COVID-19 community clusters/outbreaks are identified in an area with mink farms, enhanced testing of the population and sequencing of positive specimens is also encouraged, in order to identify possible circulating mink-related variants.

Triggers should be developed for when to initiate assessment of antigenicity and viral infectivity in viral isolates that exhibit genomic changes in areas of the genome that may influence induction of neutralising antibodies. This would facilitate preparation or agreement with reference laboratories of how and when to conduct such studies. Although genome-wide sequencing is becoming standard in all EU/EEA Member States and the UK, further development to agree upon and standardise methods for assessing antigenic changes using neutralisation antibody assays and viral infectivity is urgently needed. The ECOVID-LabNet (European COVID-19 reference laboratory network) is the forum for sharing experiences and method developments on antigenic characterisation and neutralisation assays. Panels of antibody standards and convalescent sera from naturally-infected and vaccinated individuals should be made available. To initiate monitoring of the antigenic properties of SARS-CoV-2 variants, ECDC will discuss with ECOVID-LabNet the possibility of using standardised protocols or centralised virus characterisation, including the testing of antigenic properties, in order to be able to compare results. Sera from humans or animals immunised with current vaccine candidates could be used to assess the relative effect on different vaccine candidates.

Infection prevention and control measures for mink farm workers and visitors

It is advised to limit the number of people in contact with mink and mink farms, including the avoidance of unnecessary visits, as a measure for reducing the risk of SARS-CoV-2 being introduced into the mink population and re-introduced from the mink population into the human population.

In June 2020, SARS-CoV-2 was classified as risk group 3 according to the biological agents directive[1] . Employers therefore have an obligation to keep a list of exposed workers as well as a record of exposures, accidents and incidents for at least 10 years following the end of exposure, in accordance with national laws and/or practice.

Farm workers or visitors with COVID-19 compatible symptoms should not go to the premises of mink farms.

At the facilities, including areas where there are no mink (e.g. offices) all mink farm workers and visitors (e.g. inspectors) should follow the general recommendations for the prevention of COVID-19, whether or not they have had direct contact with mink. These recommendations include hand and respiratory hygiene, physical distancing, avoiding crowded settings and wearing a face mask, especially in indoor settings where physical distancing cannot be guaranteed. Farm facilities should be well ventilated.

In accordance with the respective EU legislation, appropriate measures [82-86] should be taken by employers to ensure the health and safety of workers after a workplace risk assessment, not only for their own protection but also to help prevent the spread of the virus, and avoid contamination of non-contaminated areas, such as communal break-time and housing facilities and means of transport. Such measures should be in accordance with the legislation governing risks from biological agents at work, in particular Directive 2004/54/EC on the protection of workers from exposure to biological agents which has been implemented into national legislation in all Member States [87].

Workers should be informed, trained and provided with any additional equipment, including appropriate personal protective equipment (PPE), washing facilities or disinfectants. Given that SARS-CoV-2 has been identified in inhalable dust [48], measures to protect against dust and aerosols are indispensable and farm facilities should have appropriate ventilation in place [48,88].

The possibility of language barriers for seasonal workers at mink farms needs to be considered when hygiene and prevention measures are being implemented on the farms in general, but particularly in relation to outbreaks and follow-up activities. It should be ensured that seasonal workers receive timely information and training in a manner that makes it accessible for them.

At mink farms with suspected or confirmed outbreaks, a workplace risk assessment should be revised by employers in coordination with the health and safety committee where it was established. Appropriate measures need to be taken that include all additional risks (e.g. increased physical and mental workload due to additional tasks such as culling and the use of PPE, chemical and physical risks) and any alterations to the work process that might have an impact on the risks workers are exposed to. Workers should be informed and consulted on these measures.

PPE needs to be provided and appropriate storage facilities for PPE should be ensured. It is essential that all mink farm workers are trained in the proper use of PPE and know how to follow the procedures for putting on and safely removing PPE in the correct sequence. Hands should be washed immediately before and after removing PPE.

In addition to the application of specific preventive measures, such as dust and aerosol avoidance, appropriate ventilation and the use of appropriate cleaning methods, workers should wear respiratory protection (filtering face piece (FFP) 2/3 respirator) and eye protection (tightly-fit goggles) and wash their hands when working closely with the animals (e.g. feeding) and when cleaning farm premises [89].

Access to appropriate facilities for hand-washing, as well as disinfectants where necessary, needs to be ensured by employers. The preventive measures and PPE used by mink farm workers involved in culling should be in accordance with the national recommendations and laws relating to culling operations. The following hygienic measures should also be considered: 1) changing to clean clothes and footwear before entering the breeding (black) area, 2) taking a shower after work and 3) washing work clothes at a temperature of minimum 60°C and washing and disinfecting footwear. Appropriate procedures need to be set up to avoid any contamination of non-contaminated (white) areas. This includes the separate storage of work and street clothing, and infection prevention measures in communal break areas and housing, in particular where workers are housed on site or in shared facilities provided by employers. Measures should also be foreseen if communal transport is used.

Pelting in infected farms represents a high risk of occupational infection. During culling operations, infected animals need to be safely destroyed and farms where infections have been confirmed need to be disinfected to minimise human exposure. All operations should follow standard procedures in the respective countries in line with national occupational safety and health requirements. All disinfection needs to include measures to cover animal products and excretions.

---

[1] Commission Directive (EU) 2020/739 of 3 June 2020 amending Annex III to Directive 2000/54/EC of the European Parliament and of the Council as regards the inclusion of SARS-CoV-2 in the list of biological agents known to infect humans and amending Commission Directive (EU) 2019/1833, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32020L0739, to be transposed by Member States by 24 November 2020.

Animal testing and prevention of spread

Intensively-reared animal species, susceptible to SARS-COV-2, such as mink may act as an amplifier of the virus, leading to an increased virus biomass in the environment, and a greater risk of virus mutations and transmission within farmed mink and between mink and humans. Therefore, increased health surveillance should be considered for mink and mink farm workers and any other people in close contact with mink, especially at farms with a previous/current history of personnel with COVID-19.

National authorities should consider increasing and continuing clinical surveillance at mink farms and laboratory testing of suspected infected mink (dead or with respiratory clinical symptoms). This should include:

- farms where mink have clinical symptoms, direct detection of SARS-CoV-2 infection via throat swabs in combination with histopathology of the lungs;

- farms without clinical symptoms, where the options for testing are PCR of throat swabs from mink that have died recently, even in the absence of lesions.

Ongoing monitoring and surveillance of mink farms (repetitive testing and/or testing of dead mink on a weekly basis) should be considered, if SARS-CoV-2 exposure from humans to mink has not been excluded.

Active serological surveillance is an option for understanding if and to what extent the virus is circulating at mink farms.

The systematic genotyping of isolated SARS-CoV-2 strains in accordance with validated protocols and the sharing of genome sequences from all infected animals, in particular mink, is recommended in order to identify clusters and related variants as soon as possible. Cats and dogs, and mustelids other than minks within the fenced area, or owned by farm personnel at infected mink farms, should be considered for testing in combination with surveillance for clinical symptoms.

National authorities should consider culling mink from infected farms and destroying raw pelts in accordance with appropriate biosecurity measures. A ban on the movement of live mink and raw pelts processed in 2020 within the EU and worldwide should also be considered for as long as SARS-CoV-2 exposure from humans to mink is occurring.

Development of One Health preparedness and response strategies

Enhanced coordination between agricultural, animal health, and human health (including occupational health and safety) sectors is essential for a timely and effective response [90]. Jurisdictions with mink farms where SARS-CoV-2 is circulating – or has the potential to circulate – in animal populations should consider developing coordinated surveillance and response plans based on timely and effective information sharing. These could include joint outbreak investigation protocols and should also take into account the measures described above relating to human and animal testing, sequencing and infection prevention and control.

There is a need to increase public awareness of mink related SARS-CoV-2 prevention and control strategies. The following groups should be specifically targeted: mink producers, mink farm workers, veterinarians and veterinary staff working with mink farms and partners in the fur industry.

Limitations

The overall assessment of this event, and particularly the assessment of the public health risk of the mutations related to Cluster 5, is limited by the low number of human cases with mink-related variants reported to date. Further investigations are needed to provide better evidence. The assessment of severity is limited by the low number of cases reported and the case-based data available in order to understand the respective circumstances of the exposures and the course of the disease.

Only a small proportion of human isolates have been sequenced worldwide and therefore it might not be possible to identify a low-level spread of new mutations of concern (irrespective of whether these are mink-related) within a population at a sufficiently early stage. Sequence analysis and virus characterisation requires time to identify new virus mutants and might not be available quickly enough and therefore general response and control measures are needed to control viral spread.

There is limited laboratory information available about phenotypic properties of the variants.

The issue of mutation of SARS-CoV-2 posing a risk for vaccine efficacy and effectiveness still has to be confirmed, and further studies are needed.

Source and date of request

ECDC internal decision, 6 November 2020.

Consulted experts

ECDC experts (in alphabetic order): Cornelia Adlhoch, Erik Alm, Julien Beaute, Eeva Broberg, Orlando Cenciarelli, Margot Einöder-Moreno, Catherine Fleming, Céline Gossner, Kari Johansen, Grazina Mirinaviciute, Angeliki Melidou, Nathalie Nicolay, Diamantis Plachouras, Emily Scott, Ettore Severi, Therese Westrell.

Public health experts

Denmark: Kåre Mølbak (Statens Serum Institut - SSI).

The Netherlands: Aura Timen (National Institute for Public Health and the Environment - RIVM), Bas Oude Munnink and Marion Koopmans (Erasmus Medical Centre).

Sweden: Mia Brytting (Folkhalsomyndigheten).

European Medicines Authority (EMA): Marco Cavalieri.

European Agency for Safety and Health at Work (OSHA): Elke Schneider.

Veterinary Public Health Experts

Denmark: Anette Ella Boklund, and Søren Saxmose Nielsen (University of Copenhagen); Anette Bøtner (University of Copenhagen and Statens Serum Institut - SSI).

European Food Safety Authority (EFSA): Alessandro Broglia, Nikolaus Kriz, Yves Van der Stede.

All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.
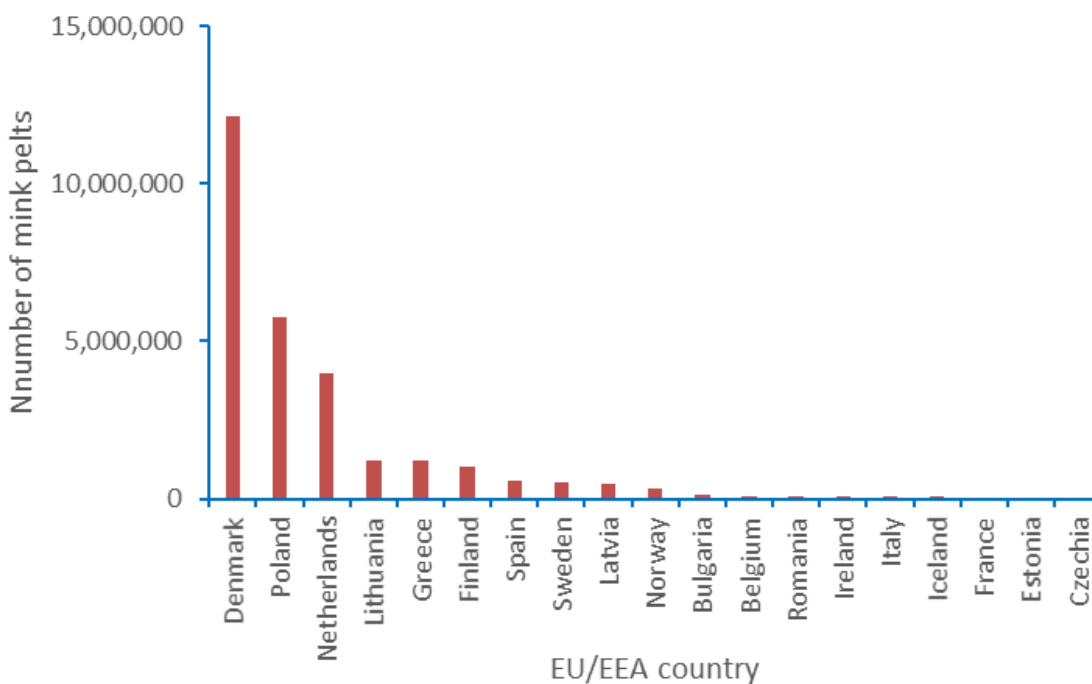
Annex 1

Figure 1. **Number of mink farms by EU/EEA country in 2019**

Note: The number of farms include a minority of fox and Finn raccoon farms.

Source: EU Fur Association https://www.sustainablefur.com/
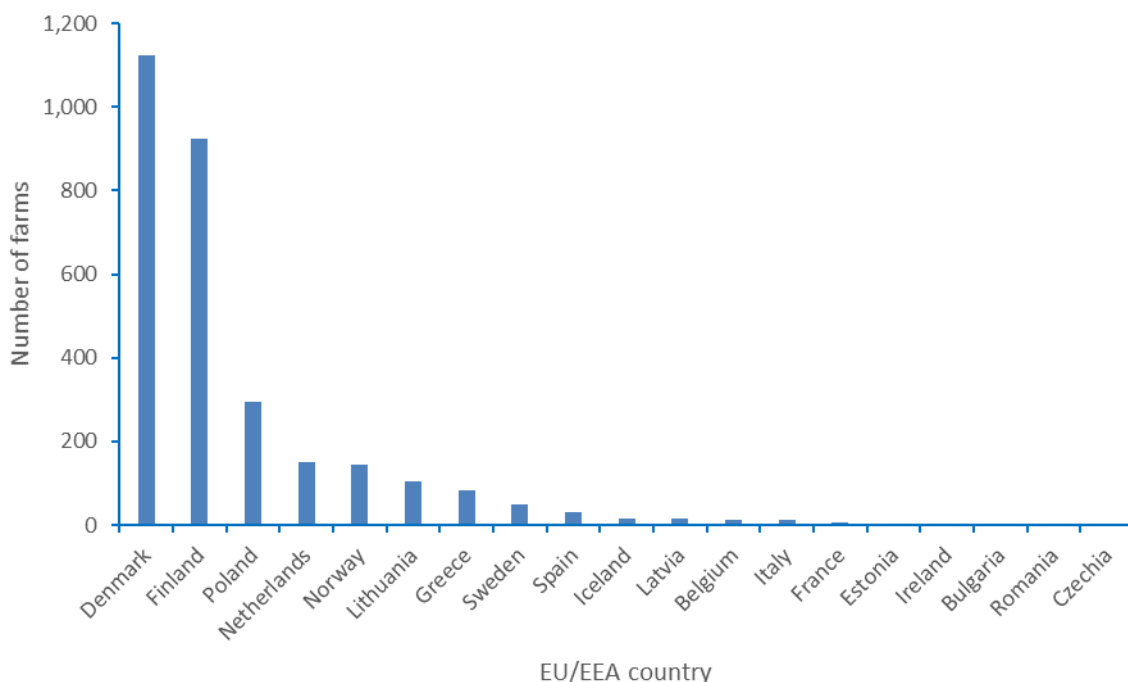
Figure 2. **Number of mink pelts produced by EU/EEA country in 2019**

Source: EU Fur Association https://www.sustainablefur.com/

Figure 3. **Mean number of animals per farm by EU/EEA country in 2019**

Source: EU Fur Association *https://www.sustainablefur.com/*
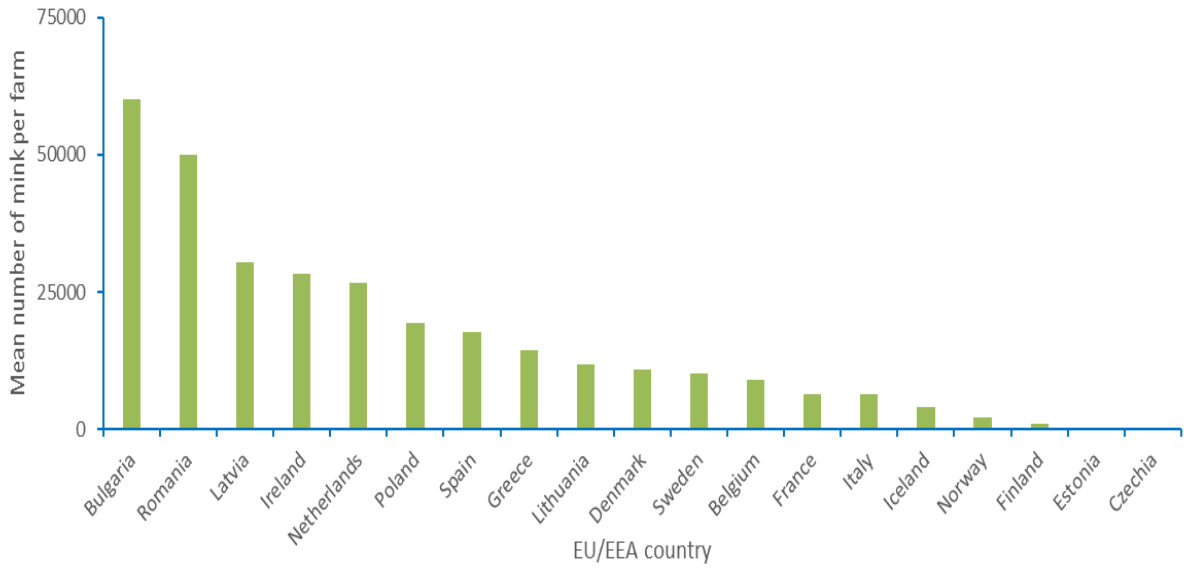
References

1. Statens Serum Institut. Risikovurdering af human sundhed ved fortsat minkavl. 3 November 2020. Copenhagen: Statens Serum Institut; 2020.

2. World Organisation for Animal Health. COVID-19 Portal. Events in animals [cited 11 November 2020]. Available from: https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/events-in-animals/

3. Lassaunière R, Fonager J, Rasmussen M, Frische A, Polacek Strandh C, Rasmussen TB, et al. Working paper on SARS-CoV-2 spike mutations arising in Danish mink, their spread to humans and neutralization data [Pre-print] Copenhagen: Statens Serum Institut; 2020. Available from: https://files.ssi.dk/Mink-cluster-5-short-report_AFO2

4. European Centre for Disease Prevention and Control (ECDC). Influenza virus characterisation, summary Europe, July 2020 Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/influenza-characterisation-report-september-2020.pdf

5. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science. 2020:eabe5901. Available from: https://science.sciencemag.org/content/early/2020/11/09/science.abe5901

6. GISAID EpiCoV database. GISAID platform [cited 11 November 2020]. Available from: https://www.gisaid.org/about-us/history/

7. Welkers MRA, Han AX, Reusken CBEM, Eggink D. [In press]. Possible host-adaptation of SARS-CoV-2 due to improved ACE2 receptor binding in mink. Virus Evolution. 2020.

8. World Organisation for Animal Health. Reporting SARS-COV-2 to the OIE Paris: OIE; 2020. Available from: https://www.oie.int/fileadmin/Home/MM/A_Reporting_SARS-CoV-2_to_the_OIE.pdf

9. World Organisation for Animal Health. Considerations for sampling, testing, and reporting of SARS-CoV-2 in animals Paris: OIE; 2020. Available from: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/Sampling_Testing_and_Reporting_of_SARS-CoV-2_in_animals_final_7May_2020.pdf

10. Colorado Veterinary Medical Association. CDC: Minks, ferrets highly susceptible to SARS-CoV-2 infections. Colorado: CVMA; 2020 [updated 11 September 2020].

11. Canadian Veterinary Medical Association. Rapid Qualitative Risk Assessment (RQRA): SARS Coronavirus 2 (SARS-CoV-2) in Farmed Mink Otawa: CVMA; 2020. Available from: https://www.canadianveterinarians.net/documents/rapid-qualitative-risk-assessment-sats-cov-2-in-farmed-mink

12. Ministry of Environment and Food of Denmark. Corona fundet i nordjyske mink Copenhagen: Ministry of Environment and Food of Denmark; 2020. Available from: https://www.foedevarestyrelsen.dk/Nyheder/Aktuelt/Sider/Pressemeddelelser%202020/Covid-19-i-nordjysk-minkbes%C3%A6tning.aspx

13. Ministry of Environment and Food of Denmark. Kort over undersøgelse for COVID-19 i mink [Internet]. 2020 [cited 2020 11 November 2020]. Available from: https://www.foedevarestyrelsen.dk/Leksikon/Sider/Kort-over-screening-af-COVID-19-i-mink.aspx

14. World Health Organization (WHO). SARS-CoV-2 mink-associated variant strain – Denmark. Geneva: WHO; 2020. Available from: https://www.who.int/csr/don/06-november-2020-mink-associated-sars-cov2-denmark/en/

15. Danish Ministry of Health. Restriktioner i Nordjylland Copenhagen: Danish authorities' joint website; 2020. Available from: https://coronasmitte.dk/restriktioner-i-nordjylland

16. Ministry of Environment and Food of Denmark. Corona-virus: Alle mink i Danmark skal aflives. 2020 [cited 11 November 2020]. Available from: https://www.foedevarestyrelsen.dk/Nyheder/Aktuelt/Sider/Nyheder%202020/Corona-virus-Alle-mink-i-Danmark-skal-aflives.aspx

17. Ministry of Health and Ministry of Agriculture, Nature and Food Quality,. Nieuwe besmetting COVID-19 bij nertsenbedrijf: Rijksoverheid; 2020 [cited 11 November 2020]. Available from: https://www.rijksoverheid.nl/actueel/nieuws/2020/11/05/nieuwe-besmetting-covid-19-bij-nertsenbedrijf

18. Netherlands Food and Consumer Product Safety Authority. Bedrijfsmatig gehouden dieren en SARS-CoV-2, 2020 [cited 11 November 2020]. Available from: https://www.nvwa.nl/nieuws-en-media/actuele-onderwerpen/corona/q/bedrijfsmatig-gehouden-dieren-en-corona

19. Italian Chief Veterinary Officer (CVO). Positive result for SARS-CoV2 in a mink herd located in Cremona Province, Lombardia Region Paris: World Organisation for Animal Health; 2020. Available from: https://www.oie.int/fileadmin/Home/MM/Italy_COVID_30.10.2020.pdf

20. El Periodico de Aragón. Detectado un brote de coronavirus en una granja de visones en Teruel Aragón: El Periodico de Aragón; 2020 [cited 11 November 2020]. Available from:

https://www.elperiodicodearagon.com/noticias/aragon/detectado-brote-coronavirus-granja-visones-teruel_1422007.html

21. Ministerio de Agricultura Pesca y Alimentacilón. Informe sobre granja de visones americanos positiva a SARS-CoV-2 en España Madrid: Ministerio de Agricultura, Pesca y Alimentacilón; 2020. Available from: https://www.oie.int/fileadmin/Home/MM/Informe_visones_OIE_16.07.20_.pdf

22. Statens veterinärmedicinska anstalt. Fler minkbesättningar smittade av coronavirus Uppsala: SVA; 2020 [11 November 2020]. Available from: https://www.sva.se/aktuellt/nyheter/fler-minkbesattningar-smittade-av-coronavirus/

23. Swedish Chief Veterinary Officer and OIE Delegate. Update from the Swedish Chief Veterinary Officer and OIE Delegate on 29 October 2020 Paris: OIE; 2020 [cited 11 November 2020]. Available from: https://www.oie.int/fileadmin/Home/MM/Sweden_Update_1_29.10.2020.pdf

24. Swedish Chief Veterinary Officer (CVO) and OIE Delegate. Information received from the Veterinary Services of Sweden on 6 November 2020 Paris: OIE; 2020 [cited 11 November 2020]. Available from: https://www.oie.int/fileadmin/Home/MM/Sweden_mink_6Nov2020.pdf

25. Associate Administrator USDA-APHIS. United States Department of Agriculture. Washington USoA. SARS-CoV-2/COVID-19, United States of America Paris: World Organisation for Animal Health (OIE); 2020. https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=36309

26. World Organisation for Animal Health. Infection with SARS-CoV-2 in animals. OIE Technical Factsheet Paris: OIE; 2020. Available from: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/A_Factsheet_SARS-CoV-2.pdf

27. Abdel-Moneim AS, Abdelwhab EM. Evidence for SARS-CoV-2 Infection of Animal Hosts. Pathogens. 2020;9(7):529.

28. Damas J, Hughes GM, Keough KC, Painter CA, Persky NS, Corbo M, et al. Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. Proceedings of the National Academy of Sciences. 2020;117(36):22311-22.

29. Richard M, Kok A, de Meulder D, Bestebroer TM, Lamers MM, Okba N et al. SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nature Communications. 2020;11(1):3496.

30. Belser JA, Barclay W, Barr I, Fouchier RAM, Matsuyama R, Nishiura H, et al. Ferrets as Models for Influenza Virus Transmission Studies and Pandemic Risk Assessments. Emerg Infect Dis. 2018;24(6):965-71.

31. Wikipedia. Mustelidae. 2020 [cited 11 November 2020]. Available from: https://en.wikipedia.org/wiki/Mustelidae

32. Bonesi L, Palazon S. The American mink in Europe: Status, impacts, and control. Biological Conservation. 2007;134(4):470-83.

33. Wikipedia. Fur farming. [cited 11 November 2020]. Available from: https://en.wikipedia.org/wiki/Fur_farming

34. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-9.

35. Nextstrain. 2020 [cited 11 November 2020]. Available from: https://nextstrain.org/

36. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27.e19.

37. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2020.

38. Simmonds P, Aiewsakun P, Katzourakis A. Prisoners of war — host adaptation and its constraints on virus evolution. Nature Reviews Microbiology. 2019;17(5):321-8.

39. Harrison TJ, Hopes EA, Oon CJ, Zanetti AR, Zuckerman AJ. Independent emergence of a vaccine-induced escape mutant of hepatitis B virus. Journal of Hepatology. 1991;13:S105-S7.

40. COVID-19 Data Portal. [cited 11 November 2020]. Available from: https://www.covid19dataportal.org/

41. Microreact. Open data visualization and sharing for genomic epidemiology. 2020 [cited 11 November 2020]. Available from: https://microreact.org/showcase

42. CoV-GLUE. 2020 [cited 11 November 2020]. Available from: http://cov-glue.cvr.gla.ac.uk/#/home

43. Su Q-D, Yi Y, Zou Y-N, Jia Z-Y, Qiu F, Wang F, et al. The biological characteristics of SARS-CoV-2 spike protein Pro330-Leu650. Vaccine. 2020;38(32):5071-5.

44. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;581(7807):221-4.

45. Thomson EC, Rosen LE, Shepherd JG, Spreafico R, da Silva Filipe A, Wojcechowskyj JA, et al. The circulating SARS-CoV-2 spike variant N439K maintains fitness while evading antibody-mediated immunity. bioRxiv: The Preprint Server for Biology. 2020:2020.11.04.355842.

46. Sternberg A, Naujokat C. Structural features of coronavirus SARS-CoV-2 spike protein: Targets for vaccination. Life Sciences. 2020;257:118056.

47. Jorquera PA, Mishin VP, Chesnokov A, Nguyen HT, Mann B, Garten R, et al. Insights into the antigenic advancement of influenza A(H3N2) viruses, 2011–2018. Scientific Reports. 2019;9(1):2676.

48. Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, et al. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Eurosurveillance. 2020;25(23):2001005.

49. Callaway E. The coronavirus is mutating — does it matter? Nature; 2020 [cited 11 November 2020]. Available from: https://www.nature.com/articles/d41586-020-02544-6

50. Hodcroft EB, Zuber M, Nadeau S, Comas I, González Candelas F, Stadler T, et al. Emergence and spread of a SARS-CoV-2 variant through Europe in the summer of 2020. medRxiv. 2020:2020.10.25.20219063.

51. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94.e9.

52. Danish Veterinary Consortium. Epidemiologisk udredning i SARS-VoV-2 smittede minkfarme Copenhagen: Danish Veterinary Consortium; 2020. Available from: https://dkvet.dk/raadgivning/raadgivningssvar/covid-19-i-mink/Epidemiologisk_udredning_i_SARS-COV-2_smittede_minkfarme_23-10-2020.pdf

53. Seow J, Graham C, Merrick B, Acors S, Pickering S, Steel KJA, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nature Microbiology. 2020.

54. Luchsinger LL, Ransegnola B, Jin D, Muecksch F, Weisblum Y, Bao W, et al. Serological Analysis of New York City COVID19 Convalescent Plasma Donors. medRxiv. 2020.

55. Crawford KHD, Dingens AS, Eguia R, Wolf CR, Wilcox N, Logue JK, et al. Dynamics of neutralizing antibody titers in the months after SARS-CoV-2 infection. The Journal of Infectious Diseases. 2020.

56. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature Medicine. 2020;26(8):1200-4.

57. Hyseni IM, Benincasa L; Piu P; Casa E; Temperton NJ, Manenti A et al. Characterisation of SARS-CoV-2 Lentiviral Pseudotypes and Correlation between Pseudotype-Based Neutralisation Assays and Live Virus-Based Micro Neutralisation Assays. Viruses. 2020;12:1011.

58. Tan CW, Chia WN, Qin X, Liu P, Chen MIC, Tiu C, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction. Nature Biotechnology. 2020;38(9):1073-8.

59. Cao Y, Su B, Guo X, Sun W, Deng Y, Bao L, et al. Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells. Cell. 2020;182(1):73-84.e16.

60. Rogers TF, Zhao F, Huang D, Beutler N, Burns A, He W-t, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science. 2020;369(6506):956-63.

61. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature. 2020;584(7819):120-4.

62. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. New England Journal of Medicine. 12 November 2020; 383:1920-1931

63. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. New England Journal of Medicine. 2020.

64. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet (London, England). 2020;396(10249):467-78.

65. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-93.

66. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586(7830):516-27.

67. CEPI. Two more laboratories join CEPI's centralised network to standardise assessment of COVID-19 vaccines. 2020 [cited 11 November 2020]. Available from: https://cepi.net/news_cepi/two-more-laboratories-join-cepis-centralised-network-to-standardise-assessment-of-covid-19-vaccines/

68. European Centre for Disease Prevention and Control (ECDC). Operational tool on rapid risk assessment methodology Stockholm: ECDC; 2019. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/operational-tool-rapid-risk-assessment-methodolgy-ecdc-2019.pdf

69. European Centre for Disease Prevention and Control. COVID-19 country overviews. Week 44, 2020 Stockholm: ECDC; 2020. Available from: http://covid19-country-overviews.ecdc.europa.eu/#10_denmark

70. European Centre for Disease Prevention and Control. Increased transmission of COVID-19 in the EU/EEA and the UK – thirteenth updatee. 23 October 2020. Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-increased-transmission-thirteenth-update#no-link

71. Williamson EJ, Walker AJ. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.

72. Sustainable fur - website. 2020 [cited 11 November 2020]. Available from: https://www.sustainablefur.com/

73. Ministry of Environment and Food of Denmark. Forvaltningsplan for mink, mårhundog vaskebjørni Danmark Copenhagen 2020. Available from: https://www.ft.dk/samling/20191/almdel/MOF/bilag/376/2154814/index.htm

74. Asferg T. Vurdering af udviklingen i bestanden af fritlevende mink i Danmark (Note from DCE - National Centre for the Environment and Energy): Aarhus Universitet; 2017. Available from: https://pure.au.dk/portal/da/persons/tommy-asferg(06ef84e9-9a04-4af2-bd17-c910eef75d5b)/publications/vurdering-af-udviklingen-i-bestanden-af-fritlevende-mink-i-danmark(d6141363-a1b1-4762-bedd-499f5a3fa9f8).html

75. Personal communication from Ministerio para la Transición Ecológica y el Reto Demográfico de España. 2020.

76. ENETWILD. 2020 [cited 11 November 2020]. Available from: https://enetwild.com/

77. Riddell S, Goldie S, Hill A, Eagles D, Drew TW. The effect of temperature on persistence of SARS-CoV-2 on common surfaces. Virology Journal. 2020;17(1):145.

78. World Organisation for Animal Health. Guidance on working with farmed animals of species susceptible to infection with SARS-CoV-2 Paris: OIE; 2020. Available from: https://www.oie.int/fileadmin/Home/MM/Draft_OIE_Guidance_farmed_animals_cleanMS05.11.pdf

79. Personal communication with colleague at University of Helsinki. 15 June 2020.

80. Wikipedia. Fur clothing. 2020 [cited 11 November 2020]. Available from: https://en.wikipedia.org/wiki/Fur_clothing

81. Wikipedia. Mink oil. 2020 [cited 11 November 2020]. Available from: https://en.wikipedia.org/wiki/Mink_oil

82. European Council. Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. 2008.

83. Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace (third individual directive within the meaning of Article 16 (1) of Directive 89/391/EEC), (2019).

84. WIKI-OSH (developed by European Agency for Health and Safety at Work - OSHA). COVID-19: Back to the workplace - Adapting workplaces and protecting workers. 2020 [cited 11 November 2020]. Available from: https://oshwiki.eu/wiki/COVID-19:_Back_to_the_workplace_-_Adapting_workplaces_and_protecting_workers

85. Commission Directive 2019/1832 of 24 October 2019 amending Annexes I, II and III to Council Directive 89/656/EEC as regards purely technical adjustments.

86. Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC), (2000).

87. Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC), (2000).

88. European Centre for Disease Prevention and Control. Heating, ventilation and air-conditioning systems in the context of COVID-19 Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/heating-ventilation-air-conditioning-systems-covid-19#no-link

89. Ministry of Environment and Food of Denmark. Forholdsregler og værnemidler Copenhagen: Ministry of Environment and Food of Denmark; 2020. Available from: https://www.foedevarestyrelsen.dk/Dyr/Dyr-og-Covid-19/Mink-og-COVID-19/Sider/Forholdsregler-og-v%C3%A6rnemidler.aspx

90. European Centre for Disease Prevention and Control. Towards One Health preparedness Stockholm: ECDC; 2018. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/One-Health-preparedness-24-May-2018.pdf