Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Corona's new coat: SARS-CoV-2 in Danish minks and implications for travel medicine

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) emerged in Wuhan, China in December 2019. Since then COVID-19 has quickly spread to more than 220 countries, affected more than 100 million people, and caused over 1.3 million deaths worldwide [1]. On the March 11, 2020 the World Health Organization (WHO) announced that COVID-19 was a global health crisis. On the same day, the Danish Government decided to lockdown Denmark, including closing the borders and introducing travel restrictions.

The initial COVID-19 epidemic in Denmark was primarily driven by travelers who have been skiing in Northern Italy and Tirol, Austria. The first Danish COVID-19 case was a journalist returning home on the February 24, 2020 from a ski holiday in Lombardy, Italy. On the March 4, 2020, the Icelandic authorities classified the ski-resort Ischgl as a high-risk area and made a notification through the *Early Warning and Response System* for the monitoring and control of infectious diseases (EWRS), operated by the European Centre for Disease Prevention and Control (ECDC). However, the Danish authorities did not declare Ischgl a COVID-19 risk-area until five days later. Consequently, numerous symptomatic Danish travelers returning from Ischgl were neither tested nor put in quarantine. A subsequent study has shown that about 70% of Danish COVID-19 cases diagnosed in April and May 2020 can be linked to Ischgl, emphasizing the role of international travel for the spread of SARS-CoV-2 [2].

In April 2020, infection with SARS-CoV-2 in mink was first reported from two mink farms in the Netherlands [3]. Current evidence indicates that the virus was transmitted to the animals through infected human workers on the farm. Transmission from human-to-mink and mink-to-human has now been well-established. Once COVID-19 reaches a mink farm it spreads very rapidly among the animals, and one worry is that infected mink herds can become a viral reservoir for new outbreaks in humans [4]. Today, infection in minks have been reported in Denmark, Netherlands, Italy, Spain, Sweden, and the United States.

Denmark is the world's largest mink fur producer in the world with 1.146 mink farms and a population of 17 million minks. In June 2020, infected minks were identified on a farm in North Jutland Region, an area with a high density of mink farms. Despite hygienic precautions and the culling of infected mink herds and uninfected mink herd on farms within a distance 7.8 km, there has been a rapid and continued spread of SARS-CoV-2 among mink farms across Denmark. Today 279 (24%) mink farms have been affected [5].

The spike protein on the surface of SARS-CoV-2 contains a receptor binding domain (RBD), which binds to angiotensin-converting enzyme 2 (ACE2), an enzyme located on the outer surface of a variety of cells. Neutralizing antibodies against the spike protein develops in >95% of COVID-19 patients. There are more than 180 SARS-CoV-2 vaccine candidates in development, the majority using the spike protein as antigen [7]. Therefore, mutations in the spike protein may have implication on immunity, risk of reinfection, vaccine efficacy and treatment with convalescent plasma.

It is a fundamental part of viral evolution that a virus will change over time and accumulate mutations, but one should be particularly concerned when viruses pass between, species, including humans and animals. When SARS-CoV-2 jumps from humans-to-mink, it will adapt to the new host – to it's new coat. A mink related variant Y453F has been found in both Denmark and the Netherlands. Y453F is located in the RBD and is probably an adaption to mink ACE2 but also increases affinity to human ACE2 and replicates as efficiently as the wildtype [8]. In Denmark, sequencing of 7108 human samples have showed mink-variants in 326 (4.6%). SARS-CoV-2 circulates rapidly in mink farms and human communities close to farms and 40% of human cases of COVID-19 cases in North Jutland Region are carrying mink-variants [7]. In the North Jutland Region five different related clusters with several mutations in the spike protein have been identified. Especially one variant "Cluster 5" has raised the alarms. Cluster 5 carries four changes in the spike protein sequence. In addition to Y453F it is 69-70delHV, I692V and M1229I [8]. Twelve human cases of infection with cluster 5 infection were identified in September 2020 in the North Jutland Region. The cases ranged in age from 7 to 79 years, and eight had a link to the mink farming industry and four cases were from the local community. The last case was diagnosed on the September 14, 2020. Based on these few cases there is no evidence that infection with Cluster 5 is associated with more severe symptoms nor changes in transmissibility [7].

Preliminary findings from The Danish Statens Serum Institut (SSI) shows that Cluster 5 may have reduced fitness as it grew slower than the wildtype and cytopathic effect was less pronounced. However, a neutralizing assay measuring activity of convalescent plasma and sera from immunized rabbits indicated a potential impact on antibody-mediated immunity, but the results need further investigations and should be confirmed before any conclusions can be drawn [8]. On the November 4, 2020, SSI shared information about cluster 5 with ECDC and WHO through EWRS and International Health Regulations. On the same day, at a press conference, the Danish prime minister informed about Cluster 5. The health authorities stated that in the "*worst case scenario, Cluster 5 could cause a second pandemic and Denmark could become the new Wuhan. In addition, vaccines under development might not be effective*". Based on the available data, that is an exaggerated conclusion. The public health action taken includes culling all farmed mink including breeding animals, locking down seven municipalities in

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North Jutland including restricting movement between these, and testing all 280.000 inhabitants and sequencing all positive samples. It turned out that the decision to kill healthy minks was without legal authority leading to mistrust to the decisions made by the government. Since the middle of September 2020, no new cases of infection with Cluster 5 have been identified and it is likely that it does not circulate any longer.

In a rapid risk assessment, ECDC states that 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 [6]. WHO states that the implications of the identified changes in cluster 5 are not yet well understood and "*advises against the application of any travel or trade restrictions for Denmark based on the information currently available on this event*" [9]. Despite this, Denmark has been taken off the UK's coronavirus travel corridor list and new rules have been introduced. British nationals, visa holders and permanent residents who have travelled to Denmark in the preceding 14 days will have to self-isolate along with their household. Other visitors travelling from Denmark will not be permitted to enter the UK. Passenger planes and ships travelling directly from Denmark, and accompanied freight, will no longer be able to land or dock at English ports. Apart from the UK, no other country, based on the cluster 5 variant situation, has changed the rules for entry of travelers arriving from Denmark [10].

This mink outbreak is "spill-over" from the human pandemic – a zoonosis in reverse. Mink appear particularly susceptible to SARS-CoV-2 and mink herds can become a reservoir for new outbreaks in humans. Therefore, culling of mink may be a necessary step to end the pandemic, but the reason should not solely be the finding of cluster 5.

In his fairytale "*It's quite true!*" the famous Danish poet HC Andersen once wrote: "It got into the papers, it was printed; and there is no doubt about it, one little feather may easily grow into five hens". Maybe cluster 5 is just another little feather that grew into five hens!

References

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[2] Bluhm A, Christandl M, Gesmundo F, et al. SARS-CoV-2 transmission routes from genetic data: a Danish case study. PLoS 2020 Oct 29;15(10):e0241405.
[3] Oreshkova N, Molenaar RJ, Vreman S, et al. SARS-CoV infection in farmed minks, The Netherlands, April and May 2020. Euro Surveill 2020 Jun;25(23):2001005.
[4] Enserink M. Coronavirus rips through Dutch mink farms, triggering culls. Science 2020;368:1169.
[5] https://www.foedevarestyrelsen.dk/Dyr/Dyr-og-Covid-19/Mink-og-COVID-19/Sider/Kort-over-kommuner-med-smittede-minkfarme.aspx.
[6] https://www.ecdc.europa.eu/sites/default/files/documents/RRA-SARS-CoV-2-in-mink-12-nov-2020.pdf.
[7] Krammer F. SARS-CoV-2 vaccines in development. Nature 2020 Oct;586(7830):516–27.
[8] https://files.ssi.dk/Mink-cluster-5-short-report_AFO2.
[9] https://www.who.int/csr/don/06-november-2020-mink-associated-sars-cov2-denmark/en/.
[10] https://www.gov.uk/foreign-travel-advice/denmark.

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