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A novel Orthonairovirus detected in grey seal (*Halichoerus grypus*)

Mikael Leijon [a,*,1], Louise Guevara [a,b,1], Gustav Averhed [a], Moa Naalisvaara Engman [a], Fereshteh Banihashem [a], Linnea Cervin [c], Britt-Marie Bäcklin [c], Neil E. Anderson [b], Siamak Zohari [a], Aleksija Neimanis [a,d]

[a] *Swedish Veterinary Agency, 751 89 Uppsala, Sweden*
[b] *The Royal (Dick) School of Veterinary Studies and The Roslin Institute, University of Edinburgh, Roslin, Midlothian EH25 9RG, UK*
[c] *Swedish Museum of Natural History, 104 05 Stockholm, Sweden*
[d] *Swedish University of Agricultural Sciences. 750 07 Uppsala, Sweden*

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ABSTRACT

The *Orthonairovirus* genus is currently markedly expanding, with several recently detected species causing febrile disease in humans. Orthonairoviruses have tripartite, negative-sense RNA genomes, with the segments denoted according to size: S, M and L. They infect birds and mammals and are primarily transmitted by ectoparasite vectors such as ticks.

In April 2020, a dead grey seal pup was found in the Östhammar municipality on the Swedish coast of the Baltic Sea. Histological examination showed pathological disruption of the normal hepatic architecture caused by fatty degeneration, necrosis and inflammation suggestive of viral hepatitis. Deep sequencing of liver, spleen, lung and brain tissue revealed the presence of a novel orthonairovirus. The complete genome was determined and showed the closest similarity to the Yezo virus, originally detected in human patients with febrile disease on Hokkaido, Japan. Phylogenetic analysis shows that this virus, for the M and L segments, belongs to a clade where many members cause febrile disease in humans. Sequence similarity for the L-segment (90%) is below the ICTV species demarcation criterion, and the species name 'Östhammar virus' is therefore proposed.

Screening with qPCR of archived liver and spleen samples from stranded seals and, as a potential ectoparasitic vector, archived ethanol-fixed seal lice, which had been collected along the same coastline, was all negative. Future work should screen the tick population in the vicinity of where the seal pup was found and investigate whether there are unexplained febrile disease cases among the human population in the area.

1. Introduction

The class *Bunyaviricetes* (previously the order *Bunyavirales*) is a large group of RNA viruses with single-stranded negative sense, or ambisense, and segmented, mainly tripartite, genomes subdivided into the orders *Elliovirales* and *Hareavirales* [1]. Bunyaviruses infect a broad range of hosts and are often vector-borne and zoonotic [2]. The *Nairoviridae* family belongs to the *Hareavirales* order and is maintained and transmitted by arthropods, mainly among birds, bats, and reptiles but also among mammals, including humans [3]. Among the seven *Nairoviridae* genera, the *Norwavirus* genus [4] and the large *Orthonairovirus* genus, which currently encompasses 64 classified species [5](https://ictv.global/report/chapter/nairoviridae/nairoviridae/orthonairovirus, accessed 2025-08-27), include viruses that can cause febrile illness in humans and livestock. Orthonairoviruses are enveloped viruses with the three segments denoted as small (S), medium (M), and large (L) gene segments. These three segments encode for, in order, the nucleoprotein (N), glycoproteins (GP, Gn, and Gc subunits), and RNA-dependent RNA polymerase (RdRp), respectively. Orthonairoviruses are predominantly tick-borne and are distinguished based on their respective dominant vector, soft ticks (family *Argasidae)* or hard ticks (family *Ixodidae*) [6,7].

From a public health perspective, the Crimean-Congo haemorrhagic fever virus (CCHFV) is the most important orthonairovirus, with an estimated 10,000–15,000 human infections each year and a case fatality rate of 5–30% [8]. In humans CCHFV can cause systemic infection, and except in blood, the virus can also be found in saliva and urine [9,10].

* Corresponding author.
E-mail address: mikael.leijon@sva.se (M. Leijon).
[1] Both authors contributed equally.

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Furthermore, although rare, human-to-human transmission can occur [11]. Many other animals can become asymptomatically infected by CCHFV [12], but as far as is currently known, only humans develop disease. On the other hand, Nairobi sheep disease virus (NSDV), which is eponymous for the *Nairoviridae* family, and the closely related Ganjam virus are significant pathogens for small ungulates [13] and also have zoonotic potential [14,15]. Furthermore, several studies have shown various orthonairoviruses, which can spill over from their natural host and infect humans, causing illnesses [16–19]. Recently there have been several outbreaks of febrile illness among humans caused by novel orthonairoviruses such as the Sōnglǐng virus [20], the Yezo virus [21], the Wetland virus [22], and the Xue-Cheng virus [23]. Otherwise, to our knowledge, no other large mammals have been reported to acquire serious illness from orthonairovirus infection.

Surveillance of seals has been part of the national environmental monitoring in Sweden since 1989. Grey seals, harbour seals and ringed seals have been observed and monitored by the Swedish Museum of Natural History (SMNH) through post-mortem examination studies and aerial population surveys [24]. Since 2020, through the directive of the Swedish Agency for Marine and Water Management (SwAM), surveillance programmes have been carried out on seals in the Baltic Sea by the SMNH and the Swedish Veterinary Agency (SVA). During these surveillance activities in April 2020, a male grey seal pup was found dead on the shore of the Baltic Sea outside Öregrund in the county of Uppsala. Necropsy examination of the seal pup revealed pathological changes consistent with viral hepatitis. Unexpectedly, metagenomic deep sequencing of the liver tissue showed high levels of a novel orthonairovirus. Here, we characterise this virus and screen for its presence in archived samples from Baltic Sea seal populations.

2. Materials and methods

2.1. Necropsy

Post-mortem examination of the grey seal pup was performed two days after arrival, following standard necropsy protocols at SVA. To assess nutritional condition, blubber thickness was measured at standard sites, including over the sternum on the ventral midline. Samples for histological examination were collected from the liver, lung, kidney, stomach, intestine, nasal mucosa, and brain and fixed in 10% neutral buffered formalin. These formalin-fixed tissues were processed and embedded in paraffin. Sections 3–4 μm thick were stained with Mayer's haematoxylin and eosin for microscopic analysis [25]. Samples for molecular analyses from the brain, lung, liver, kidney, and spleen were frozen at −20 °C. A sub-sample of spleen was later thawed, fixed in formalin and processed as above for microscopic examination.

2.2. Virus cultivation

Approximately 1 g of organ tissue was cut into small pieces using a scalpel blade. The pieces were placed into a suitable tube and homogenised in 2 mL of cell culture media using 3 mm stainless steel beads (2–5 beads/tube) by high-speed shaking for 2 min at 20 Hz in a tissue lyser. The tube was incubated at room temperature for 5 min, vortexed for 10 s, and centrifuged at 8000 ×*g* for 15 min at 4 °C. The supernatant was transferred to a new tube and stored at −80 °C until further use. The homogenate obtained from the liver sample was lightly vortexed and centrifuged at 10,000 ×*g* for 10 min at 4 °C. The supernatant was diluted 1:10 in Eagle's Minimum Essential Medium (EMEM) for inoculation onto Vero E6 cells (ATCC Cat# CRL-1586, American Type Culture Collection, Manassas, VA, USA) and in ATCC-formulated F-12 K Medium (ATCC 30–2004) for inoculation onto A549 cells (ATCC Cat# CCL-185™), with both cell cultures grown in 25 cm^2 flasks. Inoculated flasks were incubated in a humidified, 5% CO_2 incubator at 37 °C for 2 h to allow the inoculum to adsorb. After the 2 h incubation, the inoculum was discarded, cells were washed twice with PBS, and 4 mL of cell medium, supplemented with 2% fetal bovine serum and antibiotics (penicillin/streptomycin), was added. The cell cultures were maintained at 37 °C and 5% CO_2 and observed daily for cytopathic effect (CPE). After 7 days, the passaging was performed by transferring 1 mL of the supernatant to fresh cultures. During the second passage, 300 μL of cell supernatant was collected and replaced with an equal volume of cell medium at 24, 48, 72, and 96 h post passage. RNA was extracted from the collected supernatant and subjected to RT-qPCR amplification. The infected cells were harvested after seven days of incubation and lysed by three freeze-thaw cycles. The supernatant was collected by centrifugation at 10,000 ×*g* for 10 min at 4 °C. Positive results were determined by the presence of cytopathic effect and were confirmed by RT-qPCR.

2.3. Nucleic acids extraction and deep sequencing

Nucleic acids were extracted using Viral NA Magnetic Beads kits in an Arrow™ extraction robot (DiaSorin, Saluggia, Italy). For the extraction, 250 μL of the organ homogenate was digested with 10 μL of ≥800 U/mL proteinase K (Sigma-Aldrich, Saint Louis, MO, USA) and run in the extraction robot according to the manufacturer's recommendations.

Library construction was performed using the NEXTERA-XT kit (Illumina Inc., San Diego, CA, USA) following the manufacturer's instructions. The Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) was used to assess the quality of the obtained libraries. The libraries were sequenced on a MiSeq Instrument (Illumina Inc., San Diego, CA, USA) using a MiSeq Reagent Kit v3 in a 2 × 300-cycle paired-end run.

2.4. Bioinformatics

The paired-end reads were quality trimmed using Trimmomatic v. 0.39 [26] with a sliding window of four nucleotides, and an average quality score of 15 was required. The trimmed reads were assembled using Megahit v. 1.2.9 [27]. The assembled contigs were then taxonomically classified using DIAMOND v. 2.1.11 [28] with a database for classification created using the NCBI nr database of GenBank release 248 and the corresponding NCBI taxonomy databases. Maximum likelihood phylogeny was calculated using the CLC genomics workbench 24.0.2 (Qiagen Aarhus A/S, Denmark) with the following parameters: a neighbour-joining start tree was used with the Whelan and Goldman amino acid substitution model using a transition/transversion ratio of 2, 4 substitution rate categories and a gamma distribution parameter of 1. Bootstrap support was calculated using 1000 replicates.

2.5. PCR screening

2.5.1. Nucleic acids extraction

To investigate the wider occurrence of this novel orthonairovirus in seals, frozen archived tissue samples from the liver and spleen of 38 grey seals, 10 harbour seals and one ringed seal, stranded along the coasts of the Baltic Sea between 2019 and 2024, were investigated. The tissue samples were thawed and sterilely sub-sampled with the Copan Liquid Amies Elution Swab (ESwab®) Collection and Transport System and stored at −70 °C until further use. For nucleic acid extraction, the ESwab tube, containing the swab, was mixed and vortexed by shaking it gently for at least 5 s. The material was then left to settle at room temperature, after which 200 μL of the sample was transferred to a deep 96-well plate and 20 μL of proteinase K was added. For total nucleic acid extraction, the IndiMag Pathogen Kit (Indical Bioscience, Leipzig, Germany) was used on a Maelstrom 9600 (TANBead, Taoyan City, Taiwan) nucleic acid extraction robot.

Because ticks have not been documented on seals, the blood-sucking seal louse (*Echinophthirius horridus*) was investigated as a potential orthonairovirus vector. Forty-six samples of seal lice, collected from 35 grey seal and 11 harbour seal carcasses between 2004 and 2024 and fixed in 70% ethanol, were investigated. Nucleic acid extraction of the seal lice was carried out as follows. The ethanol was removed by pipetting. The sample was left to air dry for 30 min, followed by gentle washing by pipetting 500 μL water three times, and after a one-minute delay, the water was removed. Then 500 μL of TE buffer (Thermo Fisher Scientific) and 20 μL of Proteinase K were added, and the sample was freeze-thawed twice at −70 °C. Between 2 and 5 beads (2 mm steel beads and 3 mm ceramic beads) were added to the sample, which was then vigorously vortexed for 10 s and homogenised by a 20 Hz Qiagen Tissue-Lyser for 2 min. This procedure was repeated if the sample was insufficiently homogenised. The sample was then kept at room temperature for 5 min, vortexed for 10 s and again kept at room temperature for 5 min before centrifugation at 8000 ×*g* for 15 min at 4 °C. Nucleic acid extraction, as described above, was done using 200 μL of the supernatant.

2.5.2. Real-time reverse transcription PCR

PCR primers (fwd.: 5'ACCGCAAAGTATGGTCCAGG, rev.: 5'GGCCCATACTCCCGAACAAA) and a TaqMan™ probe (FAM-TCAAGTCTCAGGACAGCAGG-BHQ1), targeting the L-segment of the novel orthonairovirus, were designed using the Primer3 interface of NCBI (https://www.ncbi.nlm.nih.gov/tools/primer-blast/), under the criteria to be specific with respect to ticks and mammals. The candidate systems hereby obtained were further analysed for specificity relative to other orthonairoviruses using the CLC Genomics Workbench 24 (CLC bio, Aarhus, Denmark). A 150 nt synthetic DNA sequence (Eurofins Genomic, Denmark), covering the PCR target region, was used as a positive control, and molecular-grade water as a non-template control. The PCR experiments were carried out using the AG-Path-ID™ One-Step RT-PCR Kit (Thermo Fisher Scientific) with primer and probe at final concentrations of 15 μM and 5 μM, respectively, on a Bio-Rad C1000™ Thermal Cycler with a CFX96™ Real-Time System using the thermal profile: 45 °C for 10 min, 95 °C for 10 min, and 47 cycles of 95 °C for 15 s and 60 °C for 45 s.

3. Results

3.1. Macroscopic pathology

The male grey seal pup was 110 cm long and weighed 12.5 kg. Sternal blubber thickness was 9 mm, bony protuberances were prominent, and there were no visible internal fat stores, indicative of very poor nutritional condition. According to the size and the date when the pup was found, it was estimated to be approximately two months old. The main findings were puncture wounds in the facial region consistent with bite wounds. Five circular to oblong penetrating wounds (0.5–1 cm in diameter) were observed over the rostral region of the face, several of which were infected and exuded yellow purulent material (Fig. 1). The sinuses were also moderately filled with pus, indicative of sinusitis. Except for mild to moderate gastrointestinal parasitism, all other organs were unremarkable.

3.2. Histopathology

All fixed tissues collected were examined microscopically, and all examined organs were severely and diffusely congested. The most significant findings were seen in the liver. There was severe, diffuse hepatocellular vacuolation consistent with fatty degeneration (Fig. 2). This, combined with areas of hepatocellular rupture, single-cell necrosis, loss of hepatocytes and probable haemorrhage, disrupted the normal hepatic architecture. Hepatocellular nuclei were enlarged and often contained a large, prominent, eosinophilic nucleolus. There was infiltration of moderate numbers of mononuclear cells (lymphocytes, plasma cells and macrophages), and sporadically, some of these larger cells contained indistinct, amphophilic material in the nucleus reminiscent of inclusion bodies (Fig. 3). Focal parasitic inflammation was seen in the intestine. Except for severe congestion, no significant findings were observed in the kidney, lung, brain, stomach or nasal mucosa. Freezing artefacts precluded detailed microscopic examination of the spleen.

Fig. 1. Bite wounds exuding purulent material on the rostrum of the grey seal pup (*Halichoerus grypus*) in extremely poor nutritional condition found stranded on the east coast of Sweden on April 20, 2020.

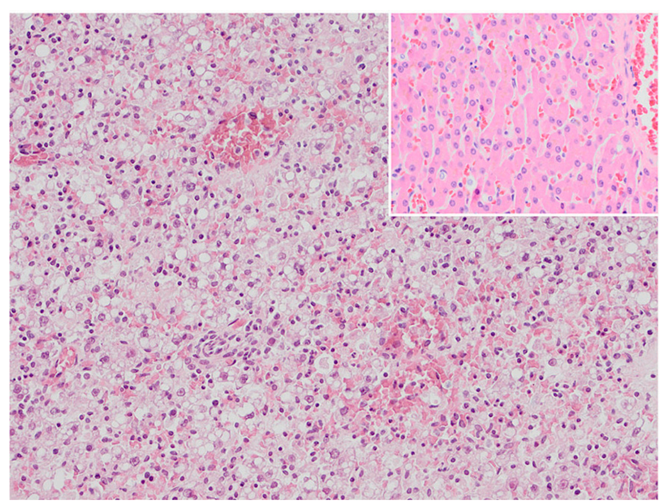

Fig. 2. Photomicrograph of liver at 200× magnification showing severely disrupted architecture. Insert: Normal liver from another seal as a comparison. HE stain.

3.3. Virus culture

The inoculum induced a CPE in both cell lines, beginning 2–4 days post-inoculation at the second passage. RT-qPCR analyses of cell culture

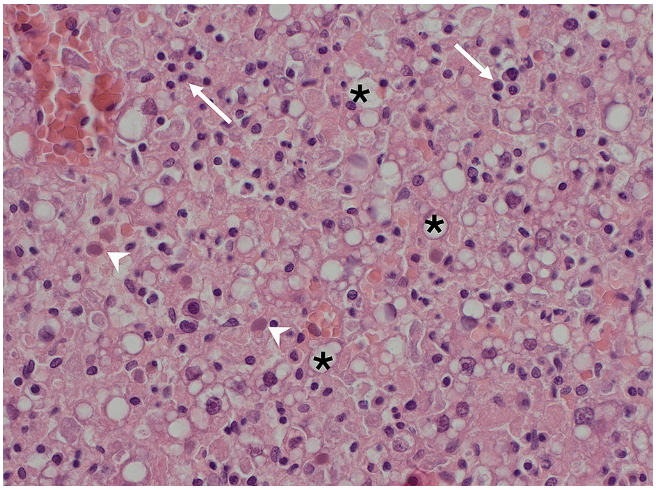

Fig. 3. Photomicrograph of liver at 400× magnification showing vacuolation of hepatocytes (black asterisk), lymphoplasmacytic inflammation (white arrow), and amphophilic intranuclear material in cells of probable histiocytic origin (white arrowhead). HE stain.

supernatants, collected at 24, 48, 72, and 96 h post-passage, showed progressively lower CT-values of 32, 27, 24, and 19, respectively, for the Vero cells and similar values for the A549 cells (data not shown). This indicates the presence of increasing amounts of the novel orthonairovirus.

3.4. Metagenomic sequencing

Samples from the liver, spleen, lung and brain were subjected to deep sequencing. Contigs classified as orthonairovirus were found in all tissues except the brain, with the largest amount of viral nucleic acids found in the liver. From the liver sample, three segments with lengths of 1686, 4180 and 12,196 nucleotides were obtained and carried a single and complete open reading frame each, as expected for orthonairoviruses. The sequences have been deposited at GenBank with accession numbers PX251549–51. The read coverage for all three segments was high, with a calculated Lander-Waterman value [29] of over 370× and a minimum of 8× coverage per nucleotide. As shown in the phylogenetic trees of Fig. 4, the virus from the grey seal consistently groups with the Yezo and Sulina viruses, with the highest similarity to the Yezo viruses. Currently, there are 44–45 complete Yezo virus CDs each for the three segments in GenBank (accessed 2025-08-25). The amino acid identity for the three the nairoviruses segments of the virus detected in the grey seal are in the ranges 88.05–88.65%, 74.74–75.11% and 89.16–90.2% for the S, M and L segments, respectively. According to the ICTV species demarcation criterion for orthonairoviruses, an amino acid identity below 93% for the L segment represents a new species (https://ictv.global/report/chapter/nairoviridae/nairoviridae/orthonairovirus). Given that the L amino acid identity of the herein described virus is less than or equal to 90.2% for all available Yezo virus sequences, it should be considered a new species. Since the grey seal pup was found in the Östhammar municipality of Uppsala County in Sweden, we propose the virus name 'Östhammar virus' and the species name *Orthonairovirus östhammarense*.

3.5. RT-qPCR screening of seals and seal lice

Screening of seal tissues and seal lice was performed using RT-qPCR to investigate the wider occurrence of this novel orthonairovirus in Baltic Sea seals and their ectoparasites. The locations of the sampled seals and lice are shown in Fig. 5. PCR results were in all cases negative for these samples although the positive control, as expected, gave a positive result.

4. Discussion

Orthonairoviruses are tick-borne pathogens capable of infecting a broad range of birds and mammals [7], but this is, to our knowledge, the first time an orthonairovirus has been found to infect a marine mammal. The ultimate death of the grey seal pup, which was in extremely poor nutritional condition and had bite wounds in the facial region, may have been multifactorial. However, the systemic orthonairovirus infection, which at least involved the liver, spleen, and lungs, was a major underlying cause. Severe pathology was observed in the liver, manifested by severe hepatic degeneration, necrosis, lipidosis and lymphoplasmacytic inflammation. Targeting of the liver and similar pathological lesions has been described in mouse infection models of other orthonairoviruses [22,30]. The liver tissue contained large amounts of virus, allowing the determination of the complete genome of all three viral segments with deep sequencing. The presence of an active virus was shown by the CPEs observed in both Vero E6 and A546 cell cultures that had been inoculated with diluted liver homogenates. Progressively larger amounts of virus over a period of four days following passaging were demonstrated by RT-qPCR. Phylogenetic comparison with other orthonairoviruses showed the highest similarity to the Yezo virus and the Sulina virus. The Yezo virus was first identified on Hokkaido, Japan [21], while the Sulina virus was found in *Ixodes ricinus* ticks in the Danube delta, Romania [31]. For the M and L segments, the herein described virus, the Yezo virus and the Sulina virus form a clade together with the Tacheng tick virus 1 [32], the Xue-Cheng virus [23] and the Songling virus [20]. These viruses form a Eurasian clade (Fig. 4), and all except the Sulina virus, which has currently only been detected in ticks, cause febrile disease in humans or, in the case of the Östhammar virus, lethal disease in a seal pup. Recently a tick screening study found variants of the Sulina virus and the Tacheng tick virus 1 in Latvia and Poland, respectively [33]. These observations taken together suggest that the prevalence of potentially pathogenic orthonairovirus in northeastern Europe may be underestimated and may pose a hitherto unknown health threat to humans and other mammals.

Despite screening liver and spleen samples from 49 seals (collected 2019–2024) and seal lice from 46 seals (collected 2004–2024) at collection sites that extended both northward and southward along the Swedish Baltic Sea coastline from where the infected seal pup was found (Fig. 5), the novel orthonairovirus was not detected in any of these samples. Transmission from another seal, potentially through the bite wounds, cannot be excluded, as seen with CCHFV, which has been detected in saliva [9,10]. Nonetheless, the problem of how the virus entered the seal population still remains. The negative screening results could be attributed to several factors: the limited stability of RNA viruses in dead tissue, the small sample size of seals and lice analysed, a single spillover event, the wide geographic area from which samples were collected and the possibility that seal louse is not a vector for the virus. In the Nordic region, blood-sucking Diptera of the *Tabanidae*, *Hippoboscidae*, *Culicidae*, *Simuliidae*, *Ceratopogonidae*, *Muscidae*, and *Rhagionidae* families are present and may potentially act as vectors. However, their association with and impact on seal colonies have not, to our knowledge, been studied. Furthermore, although some members within the *Nairoviridae* family infect other arthropods [7], all viruses within the orthonairovirus genus detected in arthropods have been identified exclusively in either hard or soft ticks (https://ictv.global/report/chapter/nairoviridae/nairoviridae/orthonairovirus). Consequently, crucial next steps are to conduct a comprehensive screening of ticks in the coastal area near where the seal pup was discovered to assess the prevalence of the novel orthonairovirus within the tick population. Additionally, investigating the occurrence of unexplained fever in the local human population is also warranted.

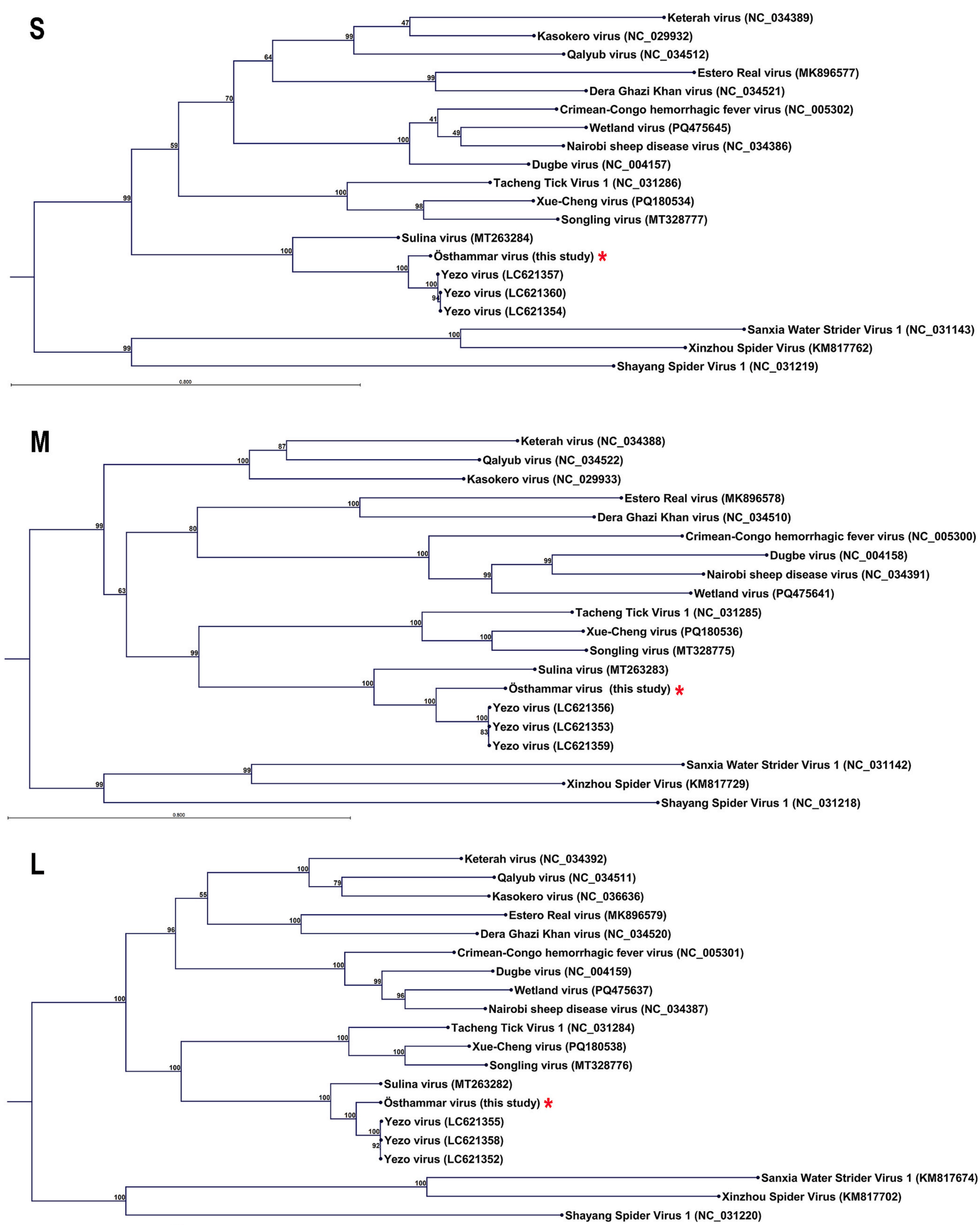

Fig. 4. Maximum likelihood phylogenetic trees were constructed for selected orthonairoviruses. The trees were inferred from an alignment of the complete amino acid sequences of the three orthonairovirus segments: S (nucleoprotein), M (glycoprotein precursor), and L (RNA-dependent RNA polymerase). The novel Östhammar virus is highlighted with an asterisk (*). The outgroup included Sānxiá water strider virus 1, Shāyáng spider virus 1, and Xīnzhōu spider virus, which belong to the genera Striwavirus, Shaspivirus, and Xinspivirus, respectively. Bootstrap values were determined using 1000 replicates and are shown at the nodes.

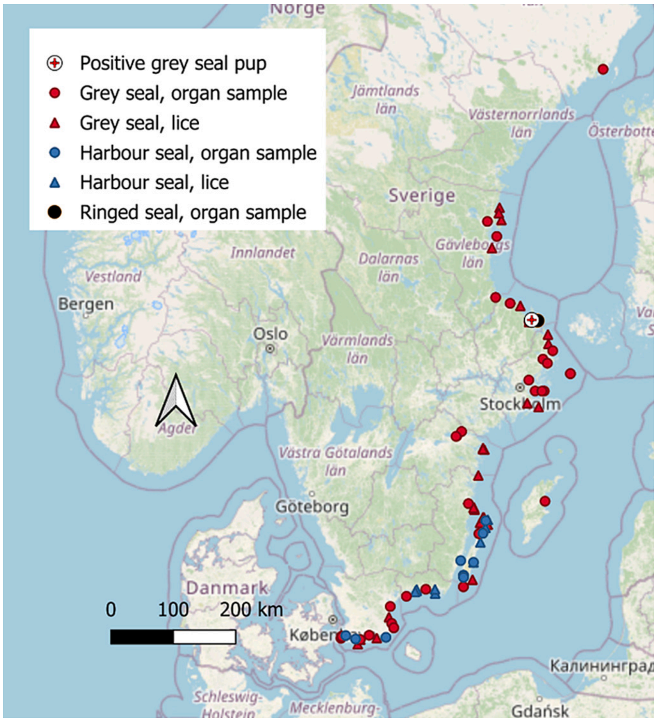

Fig. 5. Map of locations of sampled seals and lice. The grey seal infected with orthonairovirus is denoted by a red cross in a white circle. Red and blue symbols show the locations of grey seals (*Halichoerus grypus*) and harbour seals (*Phoca vitulina*), respectively. The single black symbol, partly overlapped by the red cross, shows the location of the ringed seal (*Pusa hispida hispida*). Circles indicate sites of stranded seals from which organs were analysed, and triangles show sites of seals from which lice were collected. Map data from "Open Street Map", openstreetmap.org/copyright. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

CRediT authorship contribution statement

Mikael Leijon: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Louise Guevara:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Gustav Averhed:** Writing – review & editing, Investigation. **Moa Naalisvaara Engman:** Writing – review & editing, Investigation. **Fereshteh Banihashem:** Writing – review & editing, Methodology. **Linnea Cervin:** Writing – review & editing, Investigation. **Britt-Marie Bäcklin:** Writing – review & editing, Supervision, Conceptualization. **Neil E. Anderson:** Writing – review & editing, Supervision, Conceptualization. **Siamak Zohari:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Aleksija Neimanis:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

All the authors declare that they have no competing interests.

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Data availability

The genome sequences are available at GenBank with accession numbers PX251549–51.

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