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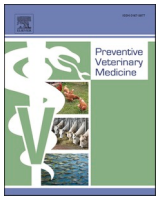

Assessing freedom from chronic wasting disease in semi-domesticated reindeer in Norway and Sweden

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ABSTRACT

Establishing freedom from disease is a key component of surveillance and may have direct consequences for trade and economy. Transboundary populations pose challenges in terms of variable legislation, efforts, and data availability between countries, often limiting surveillance efficiency. Chronic wasting disease (CWD) is a contagious prion disease of cervids. The long incubation period and slow initial epidemic growth make it notoriously difficult to detect CWD in the early phase of an epidemic. The recent emergence of CWD in wild reindeer in Norway poses a threat to approximately 250,000 semi-domesticated reindeer in Norway and 250,000 in Sweden, including transboundary populations. Here, we provide a first analysis of surveillance data (2016–2022) from all reindeer districts in Norway and Sweden to determine the probability of freedom from CWD infection. During the six years, 6017 semi-domesticated reindeer were tested in Sweden and 51,974 in Norway. Most samples came from healthy slaughtered animals (low risk). Reindeer use large and remote areas and (high risk) samples from fallen stock and animals with clinical signs were difficult to obtain. A scenario tree model was run for seven different set of values for the input parameters (design prevalence within and between districts, probability of introduction, and relative risks) to determine the effect on surveillance sensitivity. At the national level, the mean probability of disease freedom was 59.0 % in Sweden and 87.0 % in Norway by 2021. The most marked effect on sensitivity was varying the design prevalence both within and between districts. Uncertainty about relative risk ratios affected sensitivity for Sweden more than for Norway, due to the higher proportion of animals in the high-risk group in the former (13.8 % vs. 2.1 %, respectively). A probability of disease freedom of 90 % or higher was reached in 8.2 % of the 49 districts in Sweden and 43.5 % of the 46 districts in Norway for a design prevalence of 0.5 %. The probability of freedom remained below 60 % in 29 districts (59.2 %) in Sweden and 10 districts (21.7 %) in Norway. At the national level, only Norway had a sufficiently large number of samples to reach a probability of more than 95 % of disease freedom within a period of 10 years. Our cross-border assessment forms an important knowledge base for designing future surveillance efforts depending on the spatial pattern of prevalence of CWD and risk of spread.

1. Introduction

Determining the probability of freedom from disease is an important basis for mitigation and can also affect trade and economy (Christensen and Vallières, 2016). The connectivity between populations and distance to known infected populations affects the probability of

Abbreviations: BSE, bovine spongiform encephalopathy; CWD, chronic wasting disease; vCJD, variant Creutzfeldt-Jakobs disease; DP, design prevalence; EPI, effective probability of infection; RR, relative risk; RLN, retropharyngeal lymph node; SnO, test sensitivity of brainstem; SnR, test sensitivity of RLN; SnS, test sensitivity of the combined screening protocol.

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introduction of a pathogen, and hence the estimated probability of freedom (Dufour et al., 2001; Hadorn et al., 2002; Ziller et al., 2002). Transboundary populations and cross-border contacts need to be considered when estimating the probability of introduction, but this can be challenging. There may be differences between countries related to variation in legislation, data availability, surveillance effort, and format of surveillance and population data (Voyles et al., 2015). Comparative analysis of available data between countries may provide information relevant to the design of future surveillance.

Chronic wasting disease (CWD) is a fatal neurodegenerative prion disease of cervids (Haley and Hoover, 2015), similar to scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle. The infectious agents are misfolded proteins called prions. They are difficult to eliminate and can persist in the environment for many years or decades (Smith et al., 2011). CWD, as described in North America, is contagious and can spread within and between cervid populations. Animals can become infected when exposed to infectious excreta (i.e. saliva, urine, faeces) during close contact with individuals affected by CWD, or when exposed to environments contaminated with infectious material, for example, excreta or decomposed carcasses (Zabel and Ortega, 2017). After its detection in the 1960s, CWD continues to spread in wild and captive cervid populations across states in the USA and provinces of Canada with limited or no coordinated surveillance and action across borders (Uehlinger et al., 2016; Rivera et al., 2019). CWD is now well recognized as an emerging threat to cervid populations and potentially to human health in North America (Sutherland et al., 2018; Otero et al., 2021).

A key feature of contagious CWD is the long time from infection to death, lasting from 2 to 4 years or more (Johnson et al., 2011; Mitchell et al., 2012), and including a long pre-clinical phase where prions are being replicated and shed (Tamguney et al., 2009). The analytical methods available for routine diagnostics are based on the detection of abnormal prion proteins in the brain and/or lymphatic tissue from dead animals, and the sensitivity is low in the early stages of the infection. Furthermore, the low expected prevalence (<1 %) and the clustered distribution of cases in the early phases of the epidemic lead to a low probability of detection of CWD at the population level for years or decades after the first introduction in a population (Belsare et al., 2021). Hence, a fundamental challenge for efficient surveillance programs is obtaining a sufficient number of samples to assess the distribution of a disease at such a low prevalence (Heisey et al., 2014).

CWD was not known to be present in Europe until its detection in 2016 in a wild reindeer (*Rangifer tarandus*) in Nordfjella, Norway (Benestad et al., 2016). Later, cases that differ from wild reindeer cases have been detected in old moose (Hopp et al., 2024) and in red deer (Vikøren et al., 2019). The emergence of CWD in Europe opens up a range of questions about epidemiology and it has had implications on trade regulations (European Parliament and Council, 2001). With the known history of BSE, which was shown to be zoonotic and cause variant Creutzfeldt-Jakobs disease (vCJD) in humans, CWD is preemptively considered a potential public health concern (The European Commission, 2016). The nature of prion diseases makes it difficult to eradicate them once established, especially in wild populations, and the potential consequences are substantial (The European Commission, 2022). The detection of CWD in Europe led to the initiation of a 3-year surveillance program (2018–2020) for CWD in the six EU member states with populations of moose and/or reindeer populations (The European Commission, 2017). The purpose was to confirm or exclude the presence of CWD or to estimate the prevalence and geographical distribution.

The cases in wild reindeer in Nordfjella showed similarities to CWD as previously described in North America, with prions detected in both the retropharyngeal lymph nodes (RLN) and at a later stage in the brain. In an attempt to eradicate the disease and avoid spread, the first CWD detections led to depopulation of the Nordfjella zone 1 wild reindeer management area, culling and testing of more than 2000 reindeer by May 2018 (Mysterud et al., 2019b). The observed prevalence in the adult animal population (2 years and above) was 1.1 % (Mysterud et al., 2019a). The finding of CWD cases in reindeer in the Hardangervidda management area in 2020 and 2022, after intensive sampling of hunted animals (Mysterud et al., 2023), indicates spread of the disease. Therefore, the management of CWD disease in Scandinavia will be challenging in the coming years.

The potential spread of CWD to semi-domesticated reindeer would have huge animal welfare, cultural and economic consequences, with some 250,000 semi-domesticated reindeer in Norway, around 250,000 in Sweden and 200,000 in Finland (Pape and Löffler, 2012). Reindeer herding is one of the last nomadic pastoral systems carried out by indigenous people in Europe and is the key to sustaining the Sami identity, language, and traditional knowledge related to living close to nature (Holand et al., 2022; Salmi, 2022). The border between Norway and Sweden is 1630 km long and, for the most part, without fences. Historically, many reindeer herds moved between coastal summer ranges in Norway and continental winter ranges further inland into Sweden (Holand et al., 2022), and movement of animals across the border is still ongoing in many districts.

The primary objectives of this study were to assess the surveillance sensitivity and estimate the probability of freedom from CWD infection in semi-domesticated reindeer within and across borders in Norway and Sweden. These populations are partly connected from an epidemiological point of view, and this provides the main reason for analyzing the surveillance data and conducting a comparative assessment. We used scenario-tree modelling to assess the probability of semi-domesticated reindeer in Norway and Sweden being free from CWD at a low design prevalence. Secondly, we assessed the time needed to demonstrate a high probability of freedom from CWD, if we continued with the current surveillance for the years to come. Third, the results were compared between the two countries in light of the main challenges, the extent and the sensitivity of the surveillance.

2. Materials and methods

2.1. Study area and populations

Semi-domestic reindeer herds in Norway and Sweden are divided into partially overlapping administrative management units, called herding or grazing districts in Norway and ‘sameby’ in Sweden, hereafter referred to as districts (Fig. 1). Within each district, groups of reindeer owners collectively manage their reindeers in a combined herd (s). These herding alliances may persist throughout all or just part of the year, and consist of between 100 and 10,000 reindeer. Most herds move between nonoverlapping summer and winter pastures (Rivrud et al., 2018), but in some places the reindeer are largely resident, performing only local elevational migration. Most of the time, semi-domestic reindeer graze unattended and freely, using large areas. Herding is conducted during migration and, partly on a daily basis, throughout winter, when herders move their animals frequently in response to snow conditions and the presence of other herds. Herds are gathered to mark calves in summer and for slaughtering in autumn and winter (Holand et al., 2022).

In Norway there are 82 districts, of which four are in the south and have separate management from the Sami reindeer herding area of the northern districts. For Norway, the surveillance data were summarized according to year-round or summer districts. Some districts are connected through shared seasonal migration or common use of pastures. Epidemiologically connected districts were combined into one epidemiological unit, i.e. Finnmark districts were combined into six larger units and Børgefjell and Østre Namdal in Trøndelag were combined into one unit. Around 2600 tested animals, which had been registered in the Femund winter herding district, were distributed on the two districts that share winter pasture in Femund (Riast/Hylling and Essand). Similarly, in Sweden, three districts that herd together were combined (Svaipa, Malå and Gran). After aggregation, there were 46

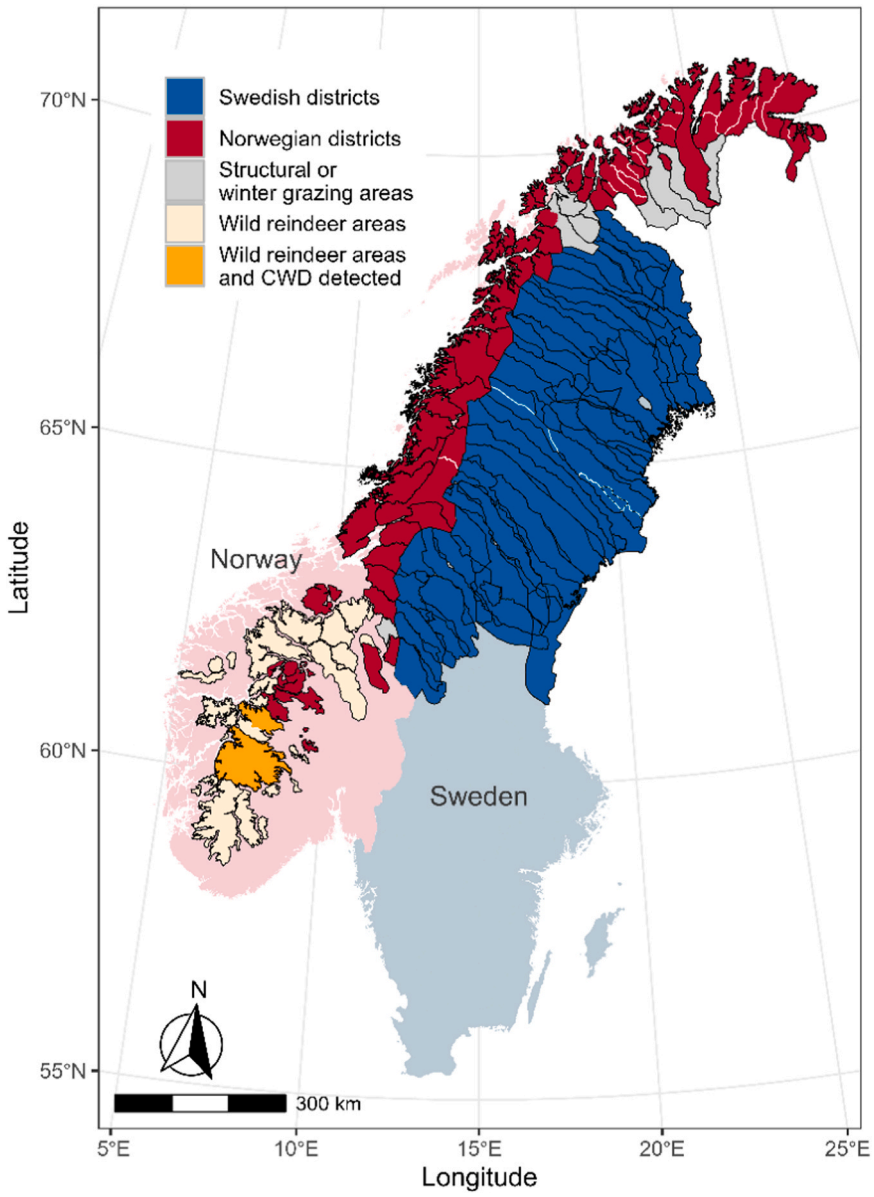

Fig. 1. Map of semi-domesticated reindeer herding districts in Norway and Sweden. The two wild reindeer areas of Hardangervidda and Nordfjella zone 1, where CWD was detected, are highlighted in orange.

epidemiological units in Norway and 49 in Sweden. Data on district borders were obtained from the County board in Sweden and from The Norwegian Institute of Bioeconomy Research (https://kilden.nibio.no). The population data for the districts in Norway came from the Norwegian Agriculture Agency. Population data were extracted from 2016 to 2019 and assumed unchanged from 2019 to 2020–21. For Sweden, population data were not available at the district level.

2.2. Sampling approaches in Norway and Sweden

After the first case of an infected wild reindeer was detected in 2016, Norway intensified testing for CWD (Våge et al., 2022), including samples from cervids when hunted or slaughtered in slaughterhouses and of fallen stock (1 year and above). The total annual number of CWD tested samples increased from 19 in 2015, >10,000 in 2016 to >33,000 in 2018, and around 35 % of the samples were from semi-domesticated reindeer. For semi-domesticated reindeer, most of the samples (97.9 %) were derived from slaughtered reindeer. From reindeer districts in the northern counties (Nordland, Troms, and Finnmark, and from 2020/2021 also Trøndelag), testing was restricted to all slaughtered animals older than 2 years, while in the southern counties, the testing included all slaughtered animals older than 1 year. From 2019/2020, there were reductions in the surveillance program and the program was aimed at 10 % of healthy slaughtered animals in northern Norway (Finnmark county). The reductions in the surveillance program were partly based on preliminary analyses using scenario-tree modelling that showed high probability of freedom of CWD in some regions, even with a design prevalence of 0.3 % (H. Viljugrein, Norwegian Veterinary Institute, unpublished results).

In Sweden, surveillance based on EU regulation (The European Commission, 2017) and focusing on animals from sampling categories with higher risk (see below) was launched in 2018. Of the total samples to be reached at the country level (6000), 2750 samples were allocated to reindeer and split equally between districts, resulting in 54 risk animals (age greater than 1 year) per reindeer district. As a consequence of the detection of CWD in moose in Sweden (Ågren et al., 2021), intensified surveillance was implemented in the geographical area surrounding the first case to investigate the occurrence and prevalence of

the disease. The intensified sampling included healthy slaughtered reindeer, which resulted in 86.9 % of the samples being slaughtered reindeer. The delimitation of the areas was decided based on moose migratory patterns, and reindeer herding areas overlapping the moose migratory area were included. The target per reindeer herding area was based on a design prevalence of 0.5–1 %.

The animal sampling categories were recorded as: 'hunted / slaughtered fit for human consumption', 'hunted / slaughtered not fit for human consumption', 'fallen / culled', 'clinical / sick' and 'road / predator killed / injured'. For semi-domesticated reindeer in Norway, samples without information on sample category were classified as 'hunted / slaughtered suitable for human consumption' (16 individuals), if tested in the main slaughter season, or 'fallen / culled' (10 individuals), if tested outside of the main slaughter season. For Norway, 690 samples tested with missing district information were excluded from the analysis, and 17.5 % of the excluded data was reported from fallen stock (including road killed).

2.3. CWD test sensitivity

The primary test was an ELISA (TeSeE® ELISA SAP, Bio-Rad, Hercules, CA, USA) until July 2020 in Norway and April 2022 in Sweden; thereafter, HerdChek BSE-Scrapie Ag Test IDEXX) was used. In Norway, the test was routinely performed on a pooled sample of brainstem (preferably from obex) and retropharyngeal lymph node (RLN) tissues. In Sweden, the brainstem and RLN tissues were tested in parallel. Samples that gave positive or inconclusive results in the primary test were analysed by Western blotting (TeSeE® Western Blot; Bio-Rad, Hercules, CA, USA) on individual tissue samples. As an approximation of the analytical test sensitivity for the ELISA tests, we used data on the sensitivity of the TeSeE® ELISA test reported from North American cervids, which was 92.5 % (81.8–97.9 %) for obex and 98.8 %

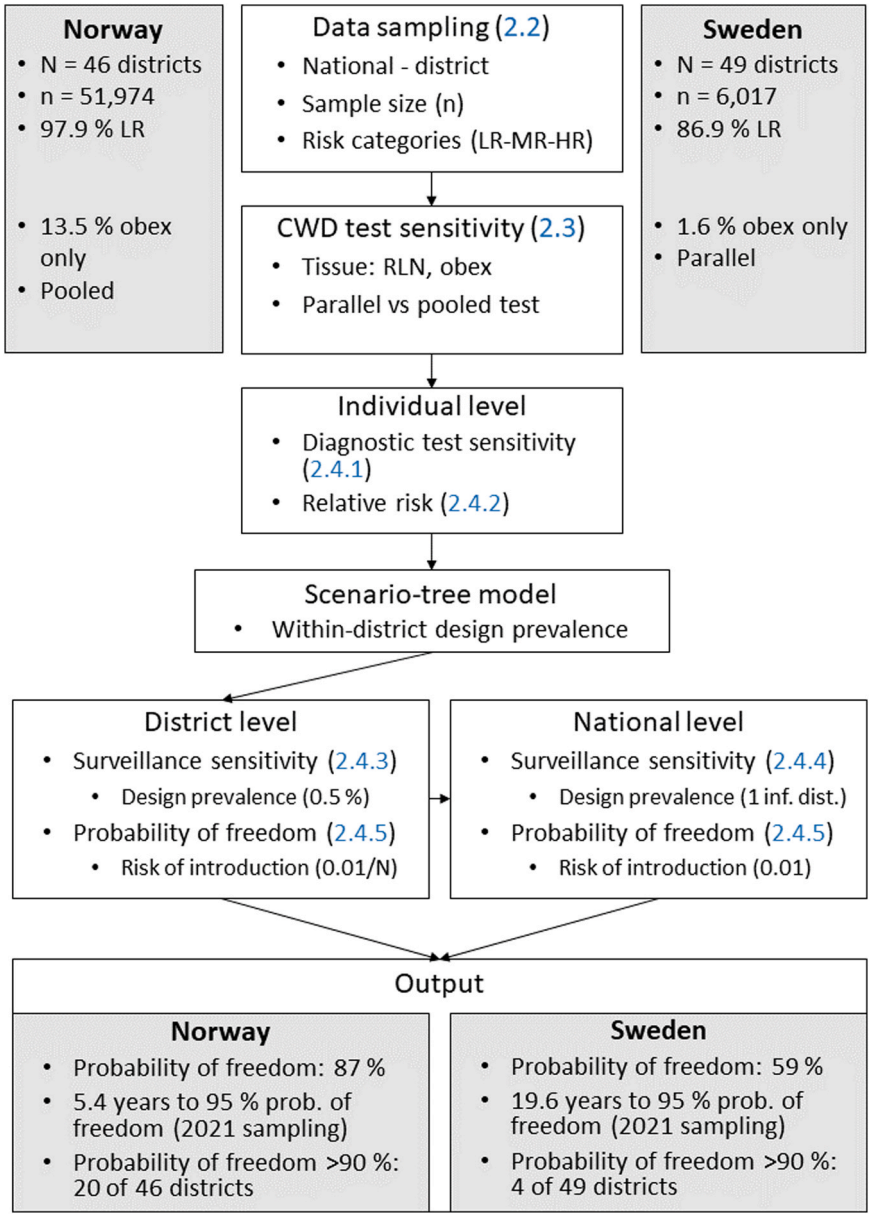

Fig. 2. An overview of the data sampling, CWD test protocol, how to account for imperfect detection and relative risk at the individual level (LR = low risk, MR = medium risk, HR = high risk) by the use of a scenario tree model to estimate surveillance sensitivity and probability of freedom. The scenario tree model was run for each district separately before the outputs were combined to calculate the national level surveillance sensitivity and probability of freedom. In the baseline model, we used a within-district design prevalence of 0.5 % and a between-district design prevalence specified by one infected district.

(93.5–99.97 %) for RLN (Hibler et al., 2003). A recent study (Mazza et al., 2023) showed that the ELISAs used in the surveillance performed well for the detection of Norwegian CWD isolates, and that the confirmatory test (TeSeE® Western Blot) confirmed all ELISA positive samples. For Norway, pooling RLN and brain tissue samples allow cost-efficient and simultaneous monitoring of different variants of CWD (with different detectability among tissues), but will have slightly lower sensitivity than analysing the two samples separately (Viljugrein et al., 2019). As a conservative approximation to account for this, we assumed that the test sensitivity was 95 % (and hence intermediate between RLN and brain tissue tested separately).

2.4. Model overview

An overview of the model framework is presented in Fig. 2. We used stochastic scenario-tree modelling to estimate surveillance sensitivity at the district and national level, as well as the probability of freedom from CWD (Martin et al., 2007). It is in principle impossible to prove true freedom from infection and the probability of freedom from infection here refers to the probability that the infection, if present, is below a certain threshold; the so-called design prevalence. Surveillance sensitivity is then the probability that the surveillance performed (or proposed) would detect at least one infected animal if the infection is present at or above the specified design prevalence.

The scenario tree model includes factors affecting the probability of infection or detection (Fig. 3), and models the process of detection by tracing the probabilities that an infected individual will yield a true positive outcome, and thereafter the detection of infection at the district level. The test sensitivity is dependent on both the infection stage and the type of tissue tested: brainstem tissue alone or brainstem tissue and RLN (Section 2.4.1). To account for the increasing detectability as the infection progresses, we randomly draw a hypothetical time since infection for each animal being tested (Viljugrein et al., 2019). For simplicity, this is presented in four stages of CWD infection in the scenario tree. Next, each animal sampled is assigned to an infection risk group (slaughtered and fit for human consumption, roadkill or fallen animal, Section 2.4.2) having different relative risk of being infected.

The main data of the scenario tree model were the number of individuals tested from different sampling categories within each district and the number of districts sampled for a specific production year. Reindeer districts (or merged districts, see above) were the epidemiological units of interest. We assumed each district had the same probability of being infected, and ran the scenario tree for each district separately, before combining the output to calculate the surveillance sensitivity and probability of freedom at national level. Estimations of the annual surveillance sensitivity at the district level (Section 2.4.3) and national level (Section 2.4.4), as well as the prior and posterior probability of disease freedom (Section 2.4.5), were performed using the R package 'freedom' (Rosendal, 2020). We also estimated the equilibrium probability of disease freedom and the time to reach 95 % posterior probability of disease freedom (Section 2.4.6). The probability of freedom from infection was estimated given no CWD cases were detected. For the present model, design prevalences were set at both the between-district (proportion of infected districts) and within-district (proportion of infected individuals) level (Section 2.4.2). For the baseline model, we chose a low design prevalence, i.e., a within-district design prevalence at 0.5 % (lower than the prevalence observed for the wild reindeer in Nordfjella) and a between-district prevalence of one district (Table 1).

2.4.1. Testing protocol and diagnostic test sensitivity

The sensitivity of the diagnostic test was modelled as a continuous function over time starting at the time of infection and ending 24 months after, when the animal is assumed to die (Viljugrein et al., 2019). This was designed to represent the increase in detectability along the long incubation period, as prions spread through different organs and in different quantities according to the stage of infection, thus leading to different test sensitivities for the two types of tissues over time. For each testing protocol, the maximum sensitivity value was obtained from values described in the literature (values used as an approximation for analytical test sensitivity, see Section 2.3). For simplicity, the test sensitivity is presented in four (0−3) stages of CWD infection in the scenario tree. At stage 0, the infection is not detectable in any tissue (Supplementary Table S1). In stage 1, the infection is detectable in RLN

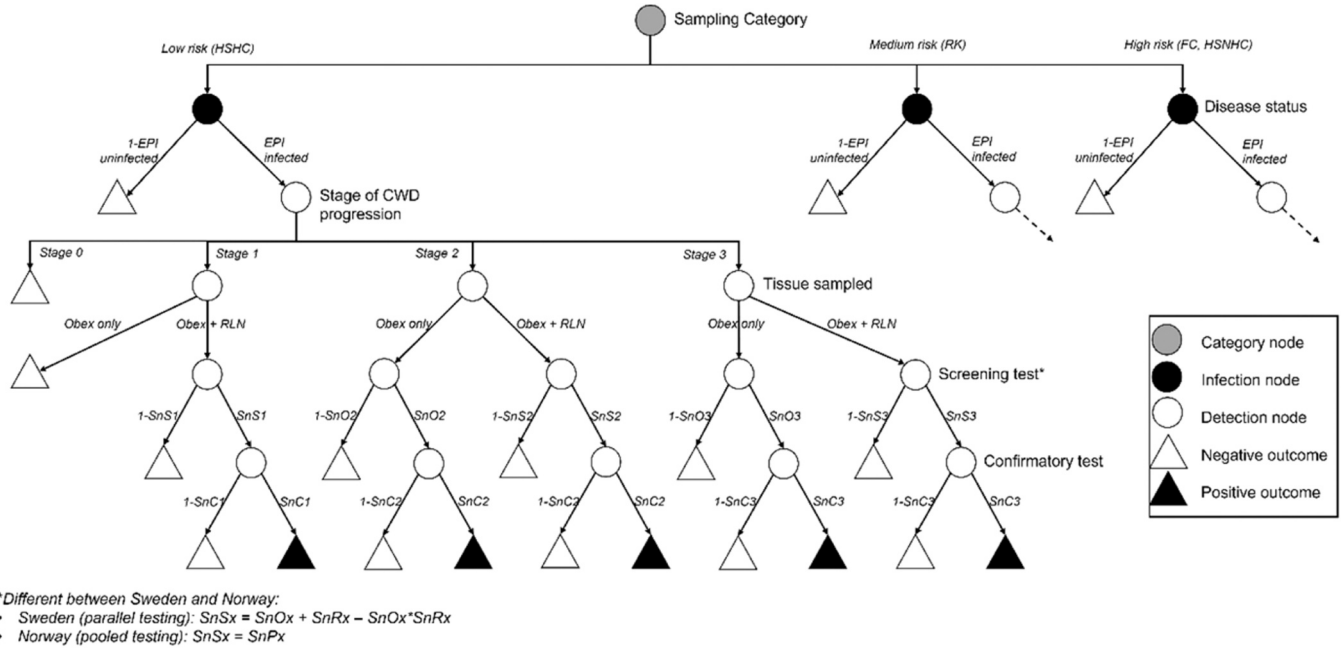

Fig. 3. Scenario tree for the CWD surveillance of semi-domesticated reindeer in a district. The test sensitivities at infection stage x are given by SnOx for the brainstem, SnRx for RLN, SnPx for testing a pooled sample of brainstem and RLN, SnSx for the combined testing of obex and RLN in parallel and SnCx for the confirmation test. Sampling categories are given by HSHC for animals hunted or slaughtered for human consumption, HSNHC for animals hunted or slaughtered not for human consumption, FC for fallen or culled animals, and RK for roadkill. EPI: effective probability of infection.

Table 1
An overview of parameter values and assumptions used in the estimation of the probability of freedom from CWD in semi-domesticated reindeer in Sweden and Norway, 2016–2021.

Parameter	Abbreviation	Baseline model	Alternate models	Source or justification
Within-district design prevalence	DP	0.5 %	1 %	Based on levels observed in Norwegian wild reindeer
Between-district design prevalence (Sweden)	BDPsw	2.04 %	4.08 %	1 (or 2) of 49 districts
Between-district design prevalence (Norway)	BDPno	2.17 %	4.35 %	1 (or 2) of 46 districts
Probability of introduction	Intro	1 %	0.1 %, 0.5 %	Assumption
Prior probability of disease freedom 2016	$PrDF_{2016}$	50 %	-	No prior knowledge of disease presence
Relative risk in high-risk group	RR_H	5	2, 3	Assumption
Relative risk in roadkill	RR_K	2	1	Alternates if roadkill is considered as increased risk or not

only, and the test sensitivity in RLN reaches its maximum in stage 2–3. In stage 2, the infection becomes detectable also in obex (minimal infection outside the obex part of the brainstem), and the test sensitivity in brainstem tissue reaches its maximum in stage 3.

In Norway, screening tests were carried out on pooled samples of both tissues (RLN and brainstem) when available (see Section 2.3), resulting in the use of a single sensitivity value. In Sweden, screening tests were conducted on both tissues in parallel, and the sensitivity of the combined screening protocol (SnS) was calculated assuming independence between the two tests. This created a total of four sensitivity curves to reflect the different testing protocols: one for RLN tissue, one for brainstem tissue, one for pooled RLN-obex/brainstem samples and one for parallel testing of RLN and obex/brainstem tissues (Supplementary material Fig. S1). Any positive results are followed by additional tests for confirmation, and the test specificity was assumed to be 100 %. We assumed 100 % sensitivity for the confirmation test. Tested animals were randomly assigned a (hypothetical) time since infection between 0 and 24 months that was matched with the corresponding sensitivity for the testing protocol (for details, see Supplementary material). Animals in the high-risk group were assigned a time since infection between 9 and 24 months, to reflect the fact that symptoms would only occur at a late stage of infection.

2.4.2. Relative risk and effective probability of infection

Normal slaughtered animals (hunted/slaughtered fit for human consumption) were considered to be in the low-risk group with a relative risk of 1. Fallen stock, animals showing clinical signs (specific and nonspecific to CWD), culled and slaughtered animals unfit for human consumption were defined as high-risk groups with relative risk (RR) values ranging from 2 to 5. Finally, road kills were considered as an intermediate group between low risk (RR=1) and moderate risk (RR=2). A summary of the input values for the scenario tree model is presented in Table 1.

Let DP denote the (within-district) design prevalence of CWD-infected animals in an infected district. In the absence of detailed knowledge on how the risk groups are represented in the overall population, it was decided to assign the selected DP to the low-risk group, and compute values of effective probability of infection (EPI) in higher risk groups by accounting for the relative risk (RR):

$$EPI = DP \times RR \tag{1}$$

As the Swedish data was composed of individual animals, these calculations were conducted for each animal individually. For Norway, with pooled district level data, a weighted average of the EPI was calculated using the proportion of animals from each risk group (see Supplementary information).

2.4.3. District level sensitivity

The district level surveillance sensitivity for the selected design prevalence was calculated as 1 minus the estimated probability of all sampled animals from the district testing negative. The calculation for Sweden was applied using individual samples, each of which had a single value for the test sensitivity and being linked to the EPI of the respective sample category. As population data were not available at the district level for Sweden, the assumption of independent samples (infinite population) was used for the calculation of district level sensitivity:

$$HSe_z = 1 - \prod_{y=1}^{n_z}(1 - (EPI_g \times SN_y)) \tag{2}$$

where: HSe_z = district level sensitivity for district z, n_z = number of animals tested in district z, EPI_g = effective probability of infection for the risk group g (low, medium, high) of animal y, SN_y = testing sensitivity of animal y.

For Norway, when the sampling was above 10 % of the population, district-level sensitivities were calculated using an approximation to the hypergeometric distribution to account for finite population (MacDiarmid, 1987), while the assumption of independence was used when the sampling was below 10 %. With data summarized at district level and the average district EPI, a simplified formula was used:

$$HSe_Z = \begin{cases} 1 - (1 - (EPI_z \times SN_z))^{n_z} & for\ n_Z \le 0.1 \bullet M_Z \\ 1 - \left(1 - \left(\frac{n_z \times SN_z}{M_z}\right)\right)^{EPI_z \times M_z} & for\ n_Z > 0.1 \bullet M_Z \end{cases} \tag{3}$$

where: SN_z = mean testing sensitivity in district z, EPI_z = mean effective probability of infection in district z, n_z = number of animals tested in district z, M_z = population size in district z.

2.4.4. National level sensitivity

To account for the finite number of districts, the surveillance sensitivity for Norway and Sweden was calculated as:

$$SySe = 1 - \prod_{z=1}^{Z}(1 - \frac{HSe_z}{Z})^{BDP \times Z} \tag{4}$$

where: SySe = national level surveillance sensitivity, Z = number of units in the system (number of districts in the country), HSe_z = surveillance sensitivity of district z, BDP = between district design prevalence.

2.4.5. Probability of freedom

The prior probability of freedom (PrDF) was calculated as the probability of freedom from last year, discounted by the probability of new introduction (see Supplementary information). For the temporal discounting of freedom probabilities, assumed probabilities of introductions in Table 1 are given at the national level. At the district level, we divided the national introduction value by the number of districts in each country (Christensen et al., 2011, 2014). In the absence of prior knowledge about disease presence in semi-domesticated reindeer in either Norway or Sweden, the prior probability of disease freedom for the first year was set to 50 % in agreement with established standards.

Then, from Bayesian portability theory, the posterior probability of freedom (PoDF) was calculated for year y as:

$$PoDF_y = \frac{PrDF_y}{1 - ((1 - PrDF_y) \times SSe_y)} \quad (5)$$

where SSe_y is the respective surveillance sensitivity for the relevant district (HSe_z) or the national level (SySe) in year y.

2.4.6. Probability at equilibrium and time to reach 95 % probability of freedom

The equilibrium probability of disease freedom and the time to reach the 95 % posterior probability of disease freedom were calculated using the R package 'epiR' (Steven, 2023). This was done for each year on the basis of the sampling frame for that year. The equilibrium probability of disease freedom refers to the mathematical limit toward which the probability of disease freedom would converge at time = infinity, if the current sampling frame from the current time point was continued unchanged (timeframe limited to 500 years).

2.5. Baseline model and variants

The baseline model was defined with a within-district design prevalence of 0.5 %, a between-district design prevalence specified by one infected district, a national annual probability of introduction of 0.01 (on average one introduction per 100 years), a relative risk for the higher risk group of 5 and a relative risk of road kills of 2. To assess the variability introduced by the randomized test sensitivity values, 1000 iterations of the baseline model were performed. We reported model outcomes by the mean of the 1000 iterations.

To test the sensitivity of the model outcome with respect to the five parameters listed above, alternative models were run with 1000 iterations, for each model variant changing the value of one parameter at a time (input values presented in Table 1). Therefore, a total of seven model variants were simulated in addition to the baseline (1 for within-district design prevalence increased to 1 %, 1 for between-district design prevalence specified by two infected districts, 2 for the probability of introduction, 2 for the relative risk of the high-risk group and 1 for the relative risk of road kills).

All calculations and figures were produced in R version 4.1.3 (R Development Core Team, 2022).

3. Results

3.1. Surveillance numbers across borders

During the six years 2016–2021, 6017 semi-domesticated reindeer were tested in Sweden and 51,974 in Norway (Table 2 and Supplementary material Table S2). A higher proportion of animals in Sweden (13.8 %) compared to Norway (2.1 %) were from higher risk groups, but the absolute number of higher risk animals were still higher in Norway due to the large sample size. A smaller proportion were only tested in brainstem tissue in Sweden (1.6 %) compared to Norway (13.5 %) (Supplementary material Table S2). Sampling in Sweden was initially very low, with 133 animals tested in the first three years, but increased in 2019 and reached its peak of 2639 in 2021. In Norway, large numbers of animals were tested from 2016 onwards, reaching a peak of approximately 14,000 in 2018 before lowering to around 6000 yearly in 2020 and 2021 (Table 2) due to reductions in the surveillance program (Section 2.2.). The sampling was not homogeneously distributed between districts. This was especially true in Sweden where in the first five years 86 % of the reindeer came from 8 of 51 districts, which were close to the locations where three CWD positive moose were detected in 2019 and 2020. The collection of samples from these districts dropped to 48 % of the total number of sampled reindeer in 2021 as the sampling increased in other areas. In Norway, despite most districts having sustained sampling throughout the years, 7 of 46 had no animals tested altogether (Supplementary material Fig. S2). These seven districts were small and had a low harvest level.

3.2. District level

In Norway, the first districts to reach a mean posterior probability of disease freedom of 0.9 or more occurred in 2017 when 12 districts reached that value. This increased to 17 in 2018, 19 in 2019, 20 in 2020 and 2021 (43.5 % of 46 districts). By 2021 another seven districts (15.2 %) were between 0.8 and 0.9 and three (6.5 %) between 0.7 and 0.8. Finally, 10 districts (21.7 %) had values below 0.6, including those seven with no testing (Figs. 4, 5, and Supplementary material Fig. S2).

In Sweden, the first district reached a mean posterior probability of disease freedom of 0.9 or greater in 2019, one more district reached this level in 2020, and this increased to four in 2021 (8.2 % of a total of 49 districts). By 2021, five other districts (10.2 %) were between 0.8 and 0.9 and three (6.1 %) were between 0.7 and 0.8. Finally, 29 districts (59.2 %) were below 0.6 (Figs. 4, 5, and Supplementary material Fig. S3). Although the randomisation of time since infection led to a high variability for the mean diagnostic test sensitivity, probability of disease freedom was less variable. On average across districts, the difference between the highest and lowest probability of freedom (%) value for a district and year was 1.3 in Norway and 0.7 in Sweden (Supplementary Table S3). The model variant 1, with the increased design prevalence (1 % instead of 0.5 %), led to increasing the number of districts with probability of freedom above 90 % in 2021 from 20 to 28 in Norway and from 4 to 10 in Sweden. However, the number of districts with probability of freedom estimated to values below 60 % remained the same at 10 in Norway and 29 in Sweden.

3.3. National level

At the national level, the high sustained and geographically distributed levels of testing in Norway led to a high mean posterior probability of disease freedom of 87.0 % in the baseline model by 2021. In Sweden, the lower volume of testing combined with more geographically focused sampling led to a lower value of 59.0 % (Fig. 6). At the national level, the stochastic simulations of test sensitivity led to very little variation in

Table 2
Yearly sampling, annual posterior probability of disease freedom, equilibrium probability of disease freedom, and time (number of years) to reach a posterior probability of 95 %. Note that year was defined to start from April.

Year	Norway				Sweden			
	Number of animals sampled	Mean probability at time of sampling (%)	Mean probability at equilibrium (%)	Time to reach 95 % (years)	Number of animals sampled	Mean probability at time of sampling (%)	Mean probability at equilibrium (%)	Time to reach 95 % (years)
2016	2557	54.0	94.2	Not reached	2	50.0		
2017	12,163	63.9	98.1	7.0	25	49.8	<50.0	Not reached
2018	14,039	72.9	98.2	6.0	106	49.8	53.4	Not reached
2019	10,643	79.6	98.0	5.0	2294	52.7	92.9	Not reached
2020	5923	83.7	97.3	7.0	952	54.0	86.9	Not reached
2021	6649	87.0	97.4	5.4	2638	59.0	96.0	19.6

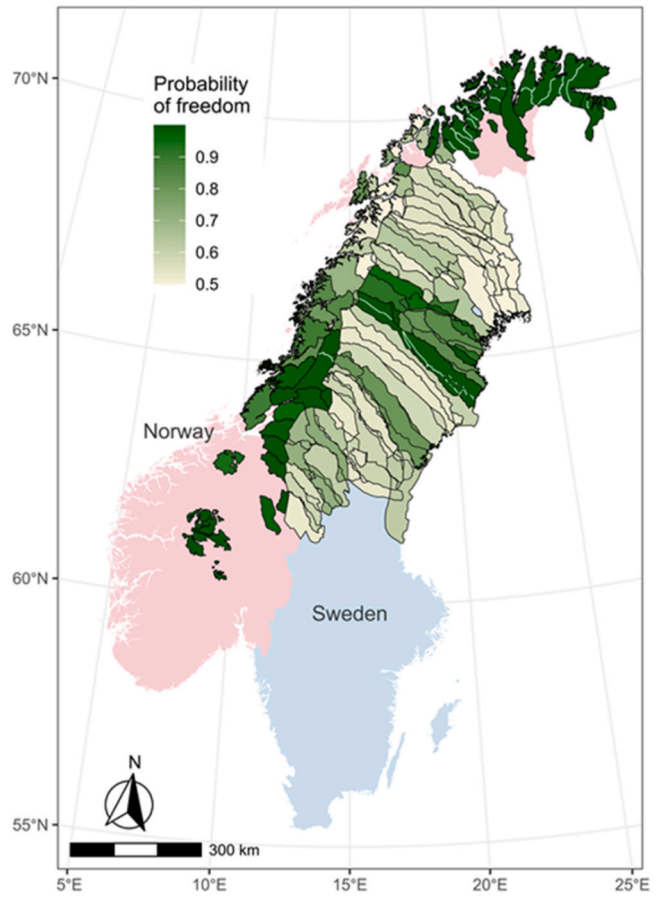

Fig. 4. Map of posterior probabilities of disease freedom (as a proportion from 0 to 1) by district in 2021. The white borders represent the borders between districts that were merged for analysis.

the estimated probabilities. The median was equal to the mean posterior probability of freedom, and the ratio between the minimum and maximum estimate was 0.998 for Norway and 0.997 for Sweden.

Of the different variants tested (Table 3), in both Norway and Sweden, the alternative value for the within-district design prevalence (1 %) and for between-district design prevalence (2 districts) had the greatest impact on the posterior probability of freedom from disease in 2021. The increase in within-district design prevalence increased the Norwegian probability of disease freedom from 87.0 % to 92.1 % and the Swedish one from 59.0 % to 64.9 % (Table 3 and Fig. 7). The increase in between-district design prevalence had an even stronger impact and brought these values to 97.5 % and 69.5 %, respectively. In comparison, a low value for national probability of introduction (0.1 %, on average 1 introduction per 1000 years) increased the Norwegian probability (%) by an absolute value of 1.9 and the Swedish one by 2.2. Changing relative risk values had very little impact in Norway, reducing the probability of disease freedom (%) by an absolute value of 0.1–0.4 compared to 0.5–1.9 for Sweden. This is due to the lower proportion of sampled animals being in higher risk groups in Norway.

3.4. Equilibrium and time to reach 95 % posterior probability of disease freedom at the national level

In Norway, for all years after 2016, sampling was sufficient to eventually reach an equilibrium of 97 % probability of freedom from CWD or more if sustained at the same level. However, as the sample numbers decreased over time, the time to reach 95 % remained stable at 5–7 years over a 5-year period instead of reducing to 2 or 3 (Table 2). In Sweden, only the year 2021 had large enough sampling numbers to eventually reach an equilibrium above 95 %, which would be reached after 19.6 years. In 2016, the sample was too small to calculate equilibrium, and in 2017 and 2018, the equilibrium was below the initial prior probability of disease freedom of 50 %, that is, the number of samples tested was too low to compensate for the risk of new introduction.

4. Discussion

The emergence of CWD in Europe raises a variety of questions about the epidemiology and occurrence of the disease. An assessment of the probability of disease detection is important to reduce uncertainties about the geographic distribution of disease, and building a robust surveillance system is a critical first step. Here, we have analysed the data of semi-domesticated reindeer tested for CWD in Norway and Sweden from 2016 to spring 2022. Our analyses revealed heterogeneous surveillance activities and lack of data standardization. Heterogeneities in surveillance efforts between and within the two countries led to a large variation in the probability of freedom from CWD between different reindeer districts, with an overall higher confidence that CWD is not present among semi-domesticated reindeer in Norway compared to Sweden.

4.1. No evidence of prevalent CWD, but variable probability of freedom

In North America, CWD has reached prevalences of 10–50 % among wild *Odocoileus* spp. deer populations (Edmunds et al., 2016; DeVivo et al., 2017), while prevalence is typically lower in elk (*Cervus canadensis*) (Monello et al., 2017; Sargeant et al., 2021). Given the lack of CWD detection despite large surveillance programs, a high prevalence of CWD is unlikely to occur among semi-domesticated reindeer in Scandinavia. However, reaching a high confidence that the CWD prevalence is lower than the design prevalence is more challenging. Therefore, it is important to note that intensive surveillance efforts reached a high probability of freedom at a low design prevalence in the districts closest to cases of CWD in wild reindeer.

A slowly increasing prevalence is typical for CWD and other diseases characterized by a long incubation period and disease course. Vague clinical signs are more likely to remain undetected compared to rapidly spreading diseases that have a short incubation period and a rapid onset of clinical signs. Populations with contagious CWD may have been present in North American deer for many years before reaching detectable levels, when relying on hunter harvest only (Belsare et al., 2020a, 2021). In particular, the first case of CWD (2020) in the Hardangervidda wild reindeer population in Norway was detected after testing more than 3500 animals (Mysterud et al., 2023), while the second case was detected in 2022 after testing another ~2700 reindeer in 2021–2022. Current screening methods that depend only on samples collected postmortem make it challenging to reach high confidence in freedom of CWD at design prevalences below 1 %.

4.2. Sensitivity and spatial distribution of sampling efforts

Our analysis showed the dominant influence of the choice of design prevalence on the calculation of disease freedom (Table 3). Setting the design prevalence, or rather deciding the level to which we want to conclude that the disease is not present, is a risk management decision that will depend on several factors. We have used a hierarchical approach to set the design prevalence on the scale between districts (one or two districts infected) and within districts (0.5 %). This is a more conservative approach than the 1 % often used in North America for a given population (Joly et al., 2009; Belsare et al., 2020b), and also in the recent EFSA report on CWD monitoring, using 3 districts infected at within-district design prevalence of 2 (or 5) % (EFSA Panel on Biological Hazards BIOHAZ, 2023).

The surveillance sensitivity at the national level was most affected by

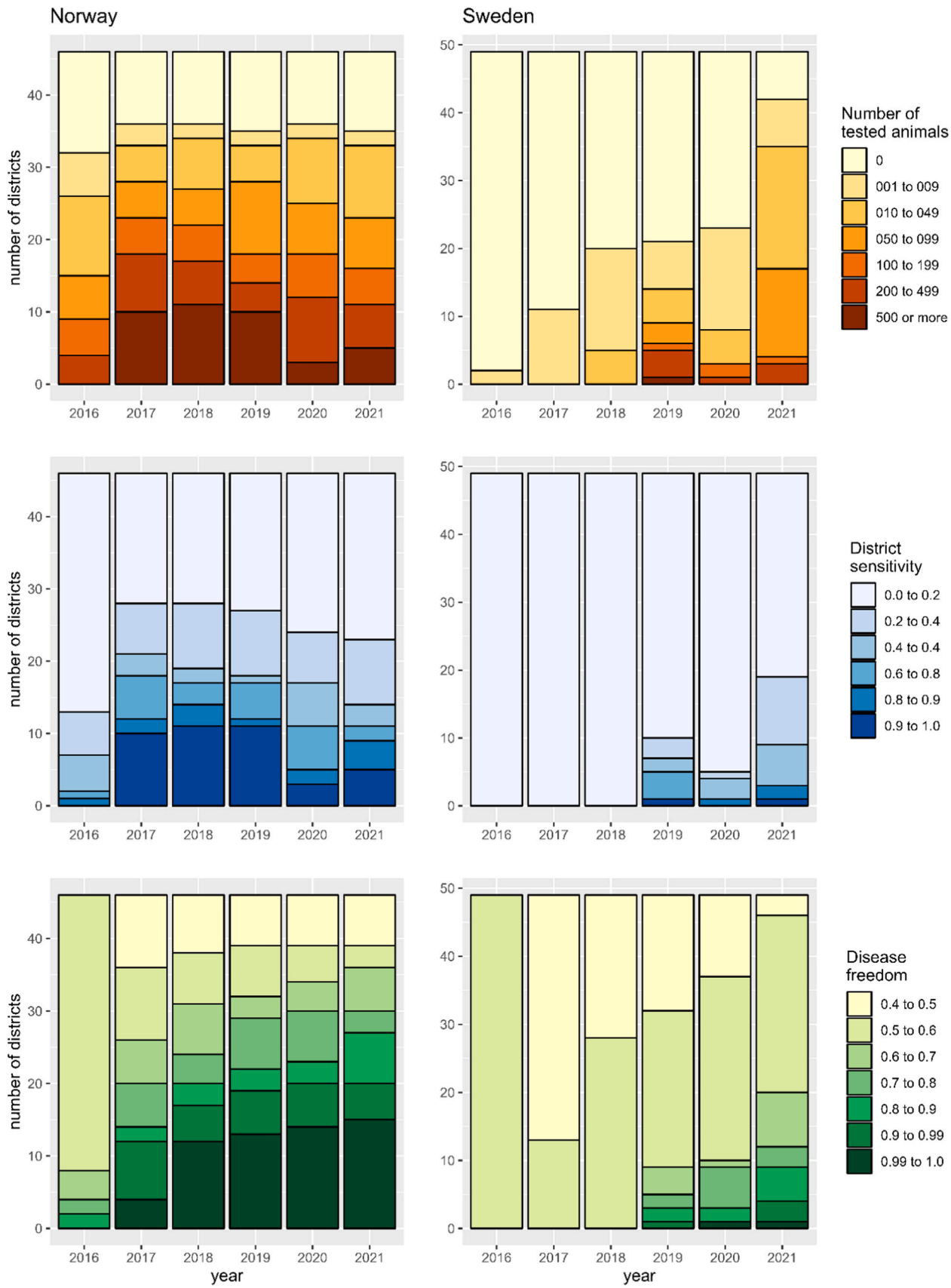

Fig. 5. Distribution of districts by sample size, district surveillance sensitivity, and posterior probability of disease freedom for each year in Norway (left) and Sweden (right).

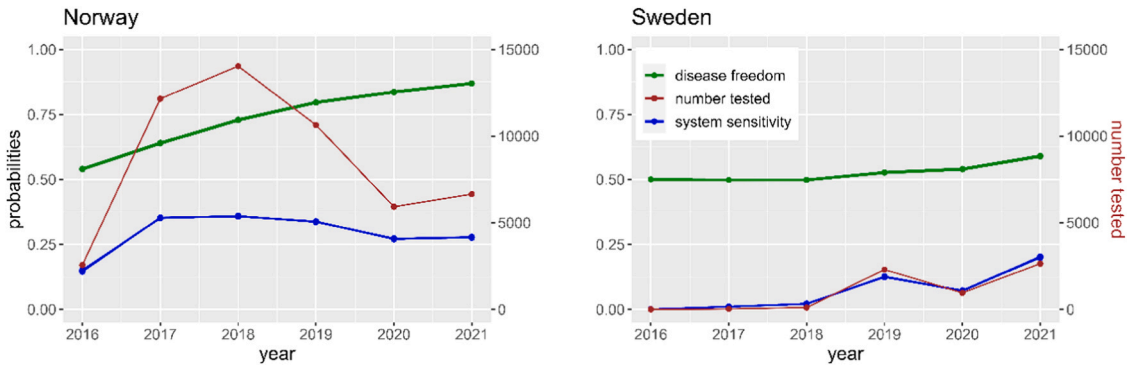

Fig. 6. Annual number of samples tested, the sensitivity of the surveillance system and the posterior probability of disease freedom from 2016 to 2021 for the baseline model for Norway (left) and Sweden (right).

Table 3
Changes in national-level probabilities of disease freedom in 2021 for model variants with different parameter settings compared to the baseline model. The baseline model was run with within-district design prevalence (DP) of 0.5 %, a between-district design prevalence (BDP) specified by one infected district, a national annual probability of introduction (Intro) of 1 % (on average one introduction per 100 years), a relative risk in the high risk group (RR_H) of 5 and a relative risk in roadkill (RR_K) of 2.

Model version	Parameter change	Mean posterior probability Norway (%)	Difference from baseline model	Mean posterior probability Sweden (%)	Difference from baseline model
Baseline		87.0		59.0	
Variant 1	DP=0.01	92.1	+5.1	64.9	+5.9
Variant 2	$BDP_{dist}=2/N_{dist}$	97.5	+10.5	69.5	+10.5
Variant 3	Intro=0.001	88.8	+1.9	61.2	+2.2
Variant 4	Intro=0.005	88.0	+1.0	60.2	+1.2
Variant 5	$RR_H=2$	86.5	-0.4	57.0	-1.9
Variant 6	$RR_H=3$	86.7	-0.3	57.7	-1.3
Variant 7	$RR_K=1$	86.9	-0.1	58.5	-0.5

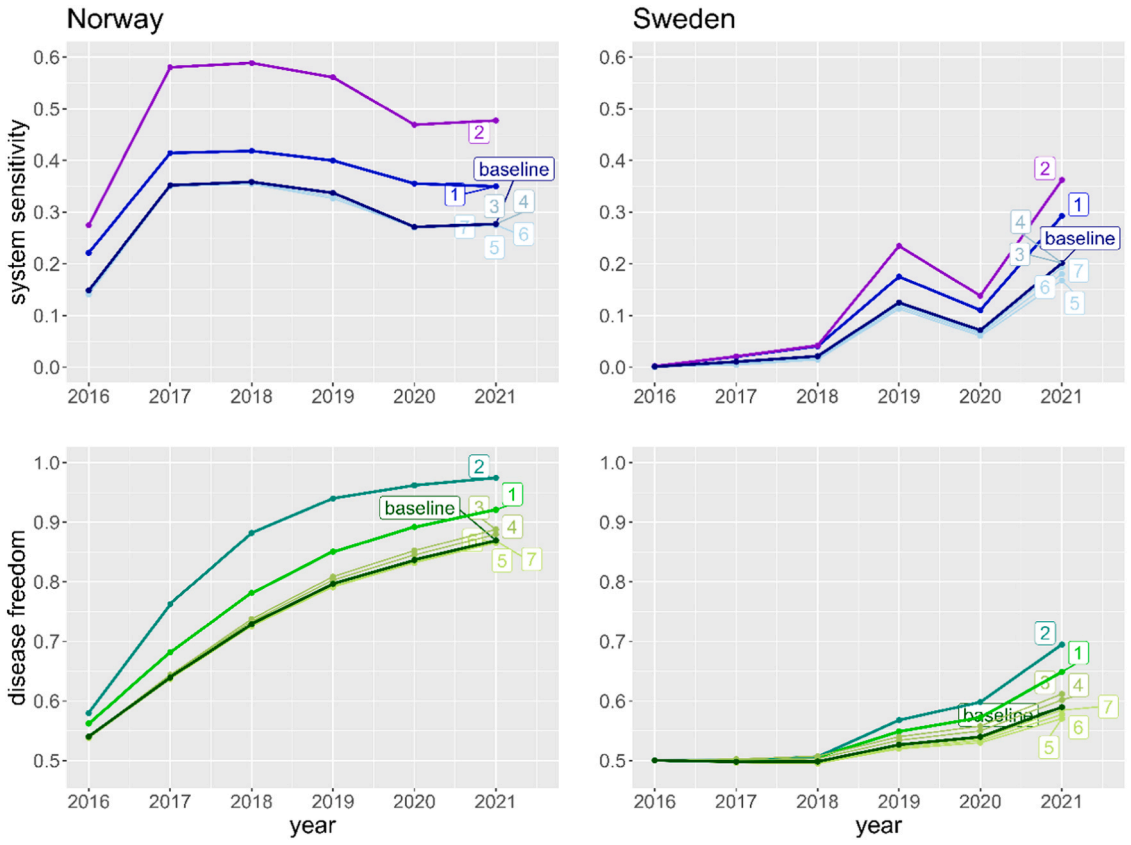

Fig. 7. The surveillance sensitivity and posterior probability of disease freedom from 2016 to 2021 for the baseline model and seven model variants for Norway (left) and Sweden (right). Numbers refer to variants in Table 3.

the design prevalence at the within- and between-district level (Table 3, Fig. 7). This hierarchical way of setting the design prevalence is common for the surveillance of diseases that are expected to cluster within farms for production animals and within regions for wild animals or farm animals in a region or country (Cameron and Baldock, 1998; Ziller et al., 2002; Frössling et al., 2008), and balancing sampling between and within districts is important for efficient surveillance. Sampling distributions could follow both individual sampling (proportional to herd size in a district) or limited sampling (a pre-fixed number per district) (Ziller et al., 2002). In practice, the surveillance was affected by several factors, e.g., economy, logistics, and focus on targeting high-risk animals which can be difficult both to detect and to sample, rather than following either of these strategies for distribution of samples across districts.

The number of samples and the targeting of the sampling differed between the countries. Our analysis revealed that a more even spatial sampling distribution would more rapidly establish freedom-from-CWD at a national scale. The lack of data from several districts markedly affected sensitivity, and the surveillance sensitivity did not increase from 2017 to 2018 in Norway despite testing a higher number of reindeer in 2018 (Fig. 6). Reindeer in some districts are not actively managed, resulting in logistical difficulties of sampling that contributed to the uneven sampling distribution. Norway initiated extensive monitoring of all cervids after the detection of CWD in wild reindeer in 2016 that far exceeded the requirements of mandatory EU monitoring.

Furthermore, the detection of sporadic cases of CWD in moose elicited intensified and spatially targeted surveillance as part of mandatory EU surveillance. Intensified surveillance in areas where moose cases were detected was one of the main reasons for the very heterogeneous sampling effort in Sweden, with limited data coming from other reindeer districts without detection in moose. This was a main cause for the different levels of certainty about the absence of low-prevalent CWD in semi-domesticated reindeer (Fig. 4). The sporadic CWD cases in moose are found in old animals, which differ from CWD found in wild reindeer cases, and appear to have a sporadic occurrence (Hopp et al., 2024).

4.3. Uncertainty about the relative risks of CWD in Europe

More efficient surveillance can be achieved by targeting risk groups and using weighted surveillance (Reist et al., 2012; Jennelle et al., 2018). Due to incomplete information for the tested animals (and population structure), only relative risk of sample category (normal slaughtered, road kills and fallen stock/culled animals unfit for human consumption) was used to define risk groups.

The EU regulatory surveillance aimed to sample high-risk animals that were not suitable for human consumption. Therefore, Sweden targeted and obtained a higher proportion of risk animals (13.8 %) than Norway (2.1 %), from which the large majority of the animals tested were from healthy slaughtered animals. This led to a higher sensitivity per sample in Sweden compared to Norway. However, this also led to a stronger effect of uncertainty about relative risk levels on sensitivity, which was more marked in Sweden (Fig. 7). Road killed mule deer (*Odocoileus hemionus*) and white-tailed deer (*Odocoileus virginianus*) in North America had a higher prevalence of CWD compared to hunted animals, but with risk ratios much lower than what was observed in clinically suspicious animals or animals found dead for other causes (Krumm et al., 2005; Jennelle et al., 2018). However, even healthy reindeer are vulnerable to vehicle collisions during winter, moving along roads and railroads to avoid deep snow and being attracted by the spread of salt on the roads (VKM et al., 2018). The extent to which risk ratios from North America are valid for our context remains uncertain, and the recent EFSA opinion advices not to include road kills in the high-risk target group (EFSA Panel on Biological Hazards BIOHAZ, 2023).

Although the target in Sweden was initially high-risk animals, they were difficult to obtain. Wild cervids and semi-domesticated reindeer utilize large and remote areas, carcasses are quickly disposed by scavengers, and the number of animals being found dead, hurt, or showing clinical signs are relatively few, difficult to detect and sample (Sleeman et al., 2012; Mysterud et al., 2023). There is a considerable potential to increase surveillance sensitivity by improving herder awareness and participation in health services. Better data registration when collecting and submitting samples would be beneficial for surveillance, and there are occasions in the reindeer management routines when suitable animals for surveillance could be identified. Gathering herds, to mark calves in summer and for slaughter in autumn/winter, and herding during winter, provide opportunities to spot individuals in poor condition, deviating in behaviour, or showing clinical signs. These individuals, if sampled, significantly increase surveillance sensitivity and probability of early detection of CWD, as demonstrated in a scenario tree model for the surveillance of CWD in the Filefjell district in Norway (Viljugrein et al., 2021). Another category of animals to target are the ones not being healthy enough to fulfil the requirements for transport to slaughter (European Parliament and Council, 2004). However, remoteness of the areas, cultural barriers, and mistrust in authorities can contribute to difficulties in implementing routines to report suspicious cases or submit samples. Another possible improvement in surveillance is related to detailed population data, which was only available on the Norwegian side of the border.

Susceptibility to CWD and other prion diseases is influenced by the gene encoding the prion protein (*PRNP*) (Robinson et al., 2012; Moazami-Goudarzi et al., 2021). Variants of *PRNP* differ in both susceptibility and pathogenesis (Johnson et al., 2011), which may in turn affect surveillance sensitivity (Viljugrein et al., 2021). However, more data and knowledge are needed before *PRNP* variants can be utilized in CWD surveillance, especially for reindeer CWD, where little genetic information is available due to the small number of cases (Güere et al., 2020).

4.4. Management of semi-domesticated reindeer and risk of introduction

The management of semi-domesticated reindeer contrasts to the management of wild and captive cervids, and hence specific challenges related to disease containment (Tryland and Kutz, 2019). Semi-domesticated reindeer are largely free-ranging most of the year, moving across vast areas like their wild counterparts. However, its human management varies between districts in terms of seasonal migration (on foot or transported by trailers), supplemental feeding during winter, extent of perimeter fencing, and level of gatherings for slaughtering that might include mixing with animals from other districts. Many of these management actions may increase or decrease disease transmission rates and geographic spread.

In the present analyses, there was no risk separation at the district level. However, our sensitivity analysis indicates that the overall risk of introduction is a major factor determining the probability of freedom from CWD, and that equilibrium may not be reached unless the sample is above a given level (Table 2). Proximity to wild reindeer areas with confirmed cases is one obvious risk factor (Viljugrein et al., 2021). Similarly, districts with more and stronger contacts with other districts have a higher risk of introduction, as has been shown for farmed deer in USA (Rorres et al., 2018). Currently, districts with low probability of freedom from CWD in Norway are small and relatively isolated, and they may not have a high risk of introduction. With more knowledge of the risk factors related to geographic connectivity, it would be reasonable to group districts according to a low, medium, or high risk for new introduction of disease, and the factors can also be managed to limit the risk of spread.

4.5. Consequences of CWD detection and future surveillance

The event of a false positive result in Børgefjell, Norway, in 2022 highlighted the far-reaching consequences a positive CWD case could have for semi-domesticated reindeer populations and for the Sami

culture, as contact tracing revealed extensive mixing of herds of several districts across the border between Sweden and Norway. Herders may fear decisions such as culling of the entire herd and a long fallowing period before restocking, similar to the situation for the Nordfjella zone 1 wild reindeer (Maraud and Roturier, 2021). Restriction on movements can disrupt seasonal grazing patterns, which in turn can require herd reduction or lead to a higher reliance on supplementary feeding. The regulation for transmissible spongiform encephalopathies in the EU (the TSE regulation) has a clear statement referring to the aim of avoiding human exposure to prions (European Parliament and Council, 2001). The zoonotic potential of CWD is regarded to be very low (Tranulis and Tryland, 2023), but recent *in vitro* and *in vivo* studies give cause for concern (Nemani et al., 2020; Hannaoui et al., 2022). In addition to direct consequences for population(s) with detection(s), the fear for the zoonotic potential may therefore negatively affect sales of meat also for nonaffected districts.

A positive case of CWD would likely increase the burdens of sampling and testing for the entire sector for decades. Decisions about future surveillance and the level of certainty of freedom from CWD to be reached will depend on future scenarios for the development of CWD and the risk of spreading, and ultimately on political will and funding. The results and experiences presented here form an important knowledge base for designing future surveillance efforts under different constraints.

CRediT authorship contribution statement

Sylvie L. Benestad: Writing – review & editing. **Jenny Frössling:** Writing – review & editing, Supervision, Project administration. **Thomas Rosendal:** Writing – review & editing, Supervision, Software, Methodology. **Petter Hopp:** Writing – review & editing, Data curation, Conceptualization. **Atle Mysterud:** Writing – review & editing, Writing – original draft, Conceptualization. **Jerome Baron:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hildegunn Viljugrein:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Maria Nöremark:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Jørn Våge:** Writing – review & editing.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Writefull in order to improve language. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of Competing Interest

We confirm that our work has not been submitted, published or accepted for publication, nor is being considered for publication elsewhere, either in whole or substantial part.

The authors declare that there is no conflict of interest. All authors have seen and approved the manuscript being submitted.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2024.106242.

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