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Review

Lessons learned and lingering uncertainties after seven years of chronic wasting disease management in Norway

Atle Mysterud[1,2], Michael A. Tranulis[3], Olav Strand[2] and Christer M. Rolandsen[2]

[1]Department of Biosciences, Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo, Oslo, Norway
[2]Norwegian Institute for Nature Research (NINA), Trondheim, Norway
[3]Department of Preclinical Sciences and Pathology, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Ås, Norway

Correspondence: Atle Mysterud (atle.mysterud@ibv.uio.no)

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Chronic wasting disease (CWD) is well known among cervids in North America. Nevertheless, management faced different types and degrees of uncertainty when CWD was first detected in reindeer *Rangifer tarandus* in Nordfjella, Norway in 2016. We present a timeline of the efforts to control CWD, and identify how the process, measurement, environmental, and implementation uncertainties developed from the onset (2016) to the current situation (2023) after seven years of CWD management. In the 'acute' phase (2016–2019), political ambitions were high and depopulation of the Nordfjella reindeer area involving marksmen aimed at eradicating CWD. Subsequently, increased surveillance and increased male harvest was used to enable early detection or to achieve 'freedom-from-CWD' status of the adjacent populations. The second phase (2020-now) came when cases were detected in the large reindeer population in Hardangervidda. Management authorities postponed culling using marksmen, signifying an important change, with more emphasis on socio-political acceptance and consideration of the negative long-term consequences of conflicts with local stakeholders. The subsequent dialogue processes between scientists and local management ended in joint advice. However, the Ministry set aside all advice in 2022, halting further actions, after pressure and negative media attention. During this period, there was no clear research plan to increase knowledge of CWD to reduce process uncertainty; however, large surveillance investments were made to reduce measurement uncertainty. Despite this, detecting and estimating CWD among reindeer at low prevalence remains a key challenge. Governance challenges have emerged as significant implementation uncertainties, partly due to the uncertain occurrence of CWD.

Keywords: management uncertainty, prion diseases, prion protein gene (PRNP), prion strains, reindeer

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Introduction

Under novel threats, natural resource management must navigate uncertainties at various levels. An established approach to addressing these challenges is the 'adaptive management' framework (Lindenmayer and Likens 2009, Westgate et al. 2013). Key features of this framework are its separation of process, measurement, environmental, and implementation uncertainties. Adaptive management typically involves deciding whether and how to respond immediately to a new situation with the knowledge and uncertainties at hand and producing a learning plan (Allen et al. 2011), that is, implement, monitor, and assess actions so that one can lower uncertainty for future decisions in an iterative cycle. However, adaptive management is often implemented passively, without an explicit plan (Westgate et al. 2013). In its original formulation, the framework has been criticized for not fully including uncertainties related to social factors (Bunnefeld et al. 2011), while many consider this an important part of implementation uncertainty (Tyre and Michaels 2011).

Management of notifiable wildlife diseases frequently involves a trade-off between responding rapidly with actions after detection, while facing uncertainties about the disease characteristics in a new setting, the occurrence, and the effectiveness of management actions to limit disease at the same time (Joseph et al. 2013). Rapid actions are frequently required to stop the further spread of the disease and limit pathogen build-up in the environment (Uehlinger et al. 2016), and social factors can make such decisions challenging to implement (Heberlein 2004). Some disease mitigation actions are intrusive and entail high costs in terms of animal welfare, economy, and lack of social acceptance. Controlling disease outbreaks and limiting pathogen spread by culling infected animals and/or preemptively culling animals considered to be at a high risk of infection can be powerful disease control strategies (Gortazar et al. 2014). Culling has been implemented to control several notifiable infectious livestock diseases (Bolzoni et al. 2014), including foot and mouth disease, classic swine fever, and classical scrapie. Examples from wildlife includes culling to control bovine tuberculosis in badger *Meles meles* (Donnelly et al. 2005), African swine fever in wild boar *Sus scrofa* (Dixon et al. 2020), brucellosis in bison *Bison bison* (White et al. 2011), and louping ill virus in red grouse *Lagopus lagopus* (Harrison et al. 2010). However, extensive culling programs are expensive to implement. If ineffective, they run the risk of being disproportional. To quote Francis Bacon: 'The remedy is worse than the disease.' Therefore, control programs in which host culling is a major constituent must navigate complex scientific and socio-political trade-offs. Implementation uncertainties include social acceptance, the effectiveness of disease control, and unintended side effects. Within the adaptive management framework, communication regarding uncertainties is important for maintaining a high level of transparency (Artelle et al. 2018), and this framework can contribute to cost-effective and evidence-based disease control strategies (Shea et al. 2014).

Chronic wasting disease (CWD) is a wildlife disease among cervids with a high socioeconomic impact (Haley and Hoover 2015, Zabel and Ortega 2017). CWD and other prion diseases are transmissible neurodegenerative diseases (TSEs) that affect humans and various livestock species (Collinge 2001). Infective agents, called prions, consist of clusters of misfolded conformers of prion proteins (Aguzzi and De Cecco 2020). Susceptibility to prions is mainly determined by a single gene encoding the prion protein (*PRNP*) (Mead et al. 2019). Prions come in different conformational variants, termed strains, and differ in their ability to misfold different variants of prion proteins encoded by the *PRNP* gene. Interspecies transmission of prion diseases is relatively rare and occurs primarily between closely related species (with similarity in *PRNP*). A game changer in the view of prion diseases was the massive outbreak of 'Mad cow disease' that peaked around 1992 in the UK, known as bovine spongiform encephalopathy (classical BSE). This has led to the emergence of variant Creutzfeldt–Jakob disease (vCJD) in some humans who consumed BSE-contaminated food products (Collinge 2001). This alarming development showed that animal prion agents can be zoonotic and cause fatal foodborne diseases in humans. Management of all prion diseases in Europe is, therefore, based on the principle of avoiding exposure of human and animal food chains to prions, which is included in the TSE regulation (European Parliament and Council 2001).

CWD was first detected in captive deer of the genus *Odocoileus* in the 1960s in Colorado but has since been detected in wild populations in 31 states of the United States and four provinces of Canada (National Wildlife Health Center 2022). There is no treatment or vaccine available for prion diseases, and there are few management options to eradicate CWD once established owing to the environmental persistence of prions (Uehlinger et al. 2016, Zabel and Ortega 2017). A characteristic feature of CWD is slow epidemic growth and an extended period of low prevalence of over a decade (Samuel 2023). Therefore, CWD is difficult to detect during the establishment phase using hunter harvests as surveillance (Belsare et al. 2021). After this stage, the prevalence in some areas increases more rapidly if not managed, can reach more than 50%, and causes a population decline after 3–4 decades, as shown for white-tailed deer *Odocoileus virginianus* (Edmunds et al. 2016) and mule deer *Odocoileus hemionus* in Colorado, USA (DeVivo et al. 2017). The detection of CWD in reindeer *Rangifer tarandus* in Norway in 2016 was the first reported case in Europe (Benestad et al. 2016). A horizon scan listed this as one of the 15 most important global issues in biodiversity and conservation research in 2018 (Sutherland et al. 2018). We faced a situation of new CWD strains in new host species and on a new continent with different ecosystems and cultures.

In this study, we used adaptive management as a framework to analyze how the four types of uncertainty (Fig. 1) have developed since the detection of CWD among reindeer in Norway in 2016, that is, after seven years of experience, monitoring, and research. We present a timeline with an overview of the main management actions with a specific

Process uncertainty	Measurement uncertainty
• Origin • Contagiousness (prion shedding) • Pathogenesis (incubation, clinical sign) • Demographic pattern (age, sex) • Susceptibility (*PRNP*) • Transmission routes (direct, environmental) • Epidemiology (transmission rate, spread) • Spillover-cervids • Zoonotic potential	• CWD case detection • CWD estimation at low prevalence • Freedom-from-CWD
Environmental uncertainty	**Implementation uncertainty**
• Environmental conditions combine with demographic stochasticity to induce random variation in epidemic growth in initial stages	• Governance (ability to implement actions) • Effectiveness (of actions in limiting CWD) • Side-effects (desired or undesired impacts)

Figure 1. Overview of the four types of uncertainties associated with CWD management in Norway. The process uncertainty can be reduced through research. Surveillance can lower measurement uncertainties but it will remain a key issue at low prevalence of CWD. Environmental uncertainty is inherent in any system. Implementation uncertainty has become increasingly important due to unpopular management actions.

focus on reindeer culling (Fig. 2), which is a key element in the management of CWD. We focused on three questions: What were the key characteristics of CWD at its first detection in 2016 (i.e. as CWD was known from North America), what have we learned about the differences between CWD observations in North America and Norway, and what key uncertainties remain as of 2023?

Review of the literature on CWD studies from Norway

We performed a systematic review of articles published in the ISI core database using the term 'CWD AND Norway NOT woody' (accessed 9 October 2023). The last term was used to avoid the literature on coarse woody debris (also with CWD as an acronym). This yielded 92 hits. One of the authors (AM) screened all titles and included original publications of relevance. Many articles did not discuss CWD (n = 26) or CWD in general but mentioned the situation of CWD in Norway (n = 24) or were reviews (n = 14). The remaining 28 articles were screened in detail and used as an overview. Of these, 13 articles were related to disease characteristics ('process'), 5 articles on methods ('measurement'), 8 on management ('implementation'), and 2 of more limited relevance.

Initial uncertainties and lessons learned

Uncertainties were expressed using the scale devised by the European Food Safety Authority (EFSA Scientific Committee et al. 2018): almost certain (99–100%), extremely likely (95–100%), very likely (90–95%), likely (66–90%), about as likely as not (33–66%), unlikely (10–33%), very unlikely (5–10%), extremely unlikely (1–5%), almost impossible (0–1%), and when relevant only a qualitative score (inconclusive, cannot conclude, unknown).

Process, structural uncertainty

Process uncertainty is related to the characteristics of CWD in individuals (Table 1) and epidemiological development and effects on population dynamics (Table 2). Knowledge about CWD is mainly derived from studies on CWD in white-tailed deer, mule deer, and elk *Cervus canadensis* in the USA and Canada (Haley and Hoover 2015, Zabel and Ortega 2017). There are four potentially susceptible wild cervid species in Norway: reindeer, moose *Alces alces*, red deer *Cervus elaphus*, and roe deer *Capreolus capreolus*, and we have limited data concerning CWD for these species. Cases of CWD have been reported in red deer (Schwabenlander et al. 2013) and moose (Baeten et al. 2007). There was also evidence from infection experiments in captive reindeer in the USA and Canada about how the infection develops in an individual depending on the *PRNP*-genotypes and that reindeer can be infected both through direct contact and through the environment (Mitchell et al. 2012, Moore et al. 2016).

What have we learned?

Histopathological (tissue distribution of pathological changes), immunohistochemical (tissue and cell distribution of proteinase K (PK)-resistant prion protein aggregates), and molecular analyses of PK-resistant (PrP^{Res}) glycoprofiles were derived from reindeer, red deer, and moose CWD cases. This provides strong evidence that at least four previously unrecognized prion strains are present in Norway, Sweden, and Finland (Pirisinu et al. 2018, Sola et al. 2023). Transmission experiments in transgenic mice and bank voles (*Myodes glareolus*) strongly support the novelty of these strains (Nonno et al. 2020, Sun et al. 2023). Hence, 1) CWD in northern Europe is not driven by a single prion strain circulating between different cervid species; 2) the prion strains observed are unlike other known animal prions, such as classical and atypical/Nor98 scrapie in sheep and, importantly, classical BSE in cattle; and 3) European CWD strains differ from their North American counterparts.

New strains create uncertainty about disease characteristics at the individual level, including patterns of prion shedding (contagiousness), incubation period, presentation and duration of clinical signs, and epidemiological characteristics. The newly detected CWD strains can be grouped into two main epidemiological 'phenotypes': 1) a novel type in moose

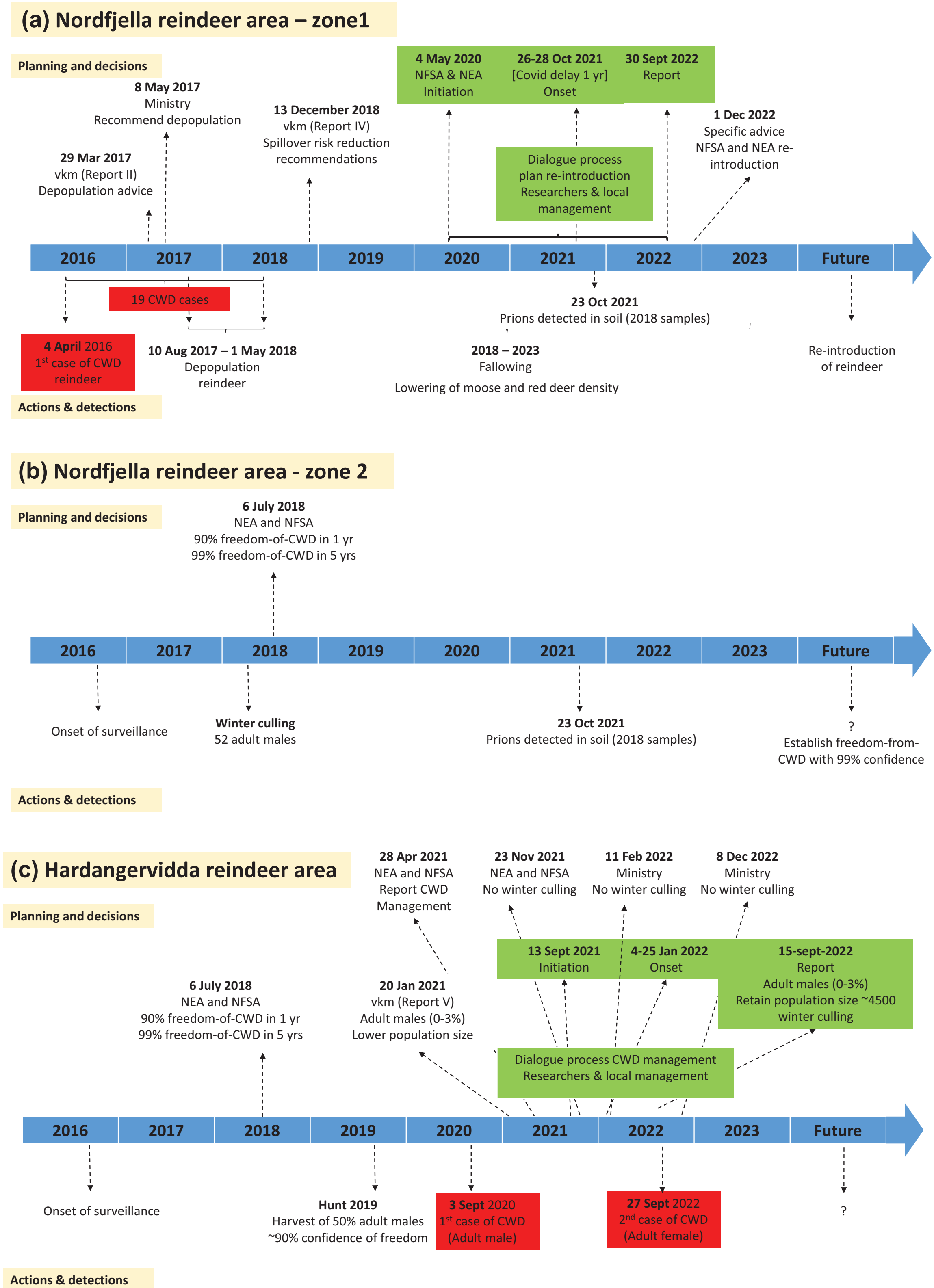

Figure 2. The timeline for the reindeer populations with CWD culling beyond ordinary surveillance of the hunter harvest. (A) Nordfjella – zone 1. (B) Nordfjella – zone 2. (C) Hardangervidda. NFSA: Norwegian Food Safety Authority; NEA: Norwegian Environment Agency; VKM: Norwegian Scientific Committee for Food and Environment; Ministry: Climate and Environment and Agriculture and Food.

Table 1. An overview of process uncertainties related to disease characteristics for CWD in reindeer in Norway. Hypotheses/predictions come from knowledge of CWD in the USA/Canada and other prion diseases. The scale of uncertainty follows EFSA (methods).

Characteristic	Hypotheses/predicted pattern from USA/Canada	Observation Norway	Status 2023 (evidence/reference)
Origin	Import of CWD prions	Novel strain	Unlikely/very unlikely (Nonno et al. 2020), at least not recent import
	From scrapie	Different molecular weight, no previous evidence of spillover to cervids	Unlikely/very unlikely (transmission experiments to sheep ongoing)
	Evolved from sporadic cases of CWD	Extensive gnawing of antlers; higher exposure	Likely (Mysterud et al. 2020d)
Contagiousness	Contagious when lymph nodes infected	Lymph nodes always infected	Almost certain (Benestad et al. 2016)
	Shedding of prions	Indirectly, with many cases in Nordfjella	Almost certain (indirect evidence)
Pathogenesis	Lethality 100% (if living long enough)	One observed dying of infection under stress	Almost certain
	Infection-to-death 2–3 years (*PRNP*-dependent)	1.5 year infected; 2.5 old infected in brain. One 3–4 year old deer dying of infection; 47.4% RLN+ only	Likely for 'wt' *PRNP* (Anecdotal evidence)
	Clinical period from weeks to two months	One drooling and aggressive deer observed; first case was drooling	About as likely as not (Anecdotal evidence)
Demographic pattern	Age (calves < yearlings < adults)	No reindeer calves, 1 yearling and adults of all ages (n = 19)	Almost certain (Mysterud et al. 2019a)
	Sex (2–3 × males > females)	Reindeer males 2.7× higher infection than females	Very likely (Mysterud et al. 2019a)
Susceptibility	'wt' *PRNP* susceptible	*PRNP* genotypes including alleles 'wt' or 'deletion' susceptible	Almost certain (Güere et al. 2020)
	No fully robust *PRNP* for CWD (fully robust *PRNP* known for sheep)	No cases among *PRNP* genotypes with only 225Y, 176D and 2M129S169M.	About as likely as not (Güere et al. 2020)

and red deer with sporadic occurrence, and 2) a new contagious variant in reindeer. The main distinction is the absence or presence of detected prions in the lymph nodes, which indicates prion shedding and, therefore, contagiousness.

New 'phenotypes' of CWD in moose and red deer with sporadic occurrence (sCWD)

With the onset of CWD surveillance, previously unrecognized types of CWD were detected in two old moose cows in 2016 (Pirisinu et al. 2018) and an old red deer hind in 2017 (Vikøren et al. 2019). In both species, prions were only detected in the brain and not in the lymph nodes using standard diagnostic tools, which indicates no (or limited) shedding of prions into the environment. Some disease characteristics appear similar to atypical forms of prion disease, with sporadic occurrences found in older small ruminants (Benestad et al. 2003) and cattle (Biacabe et al. 2004). Several subsequent cases in Sweden and Finland documented that this was restricted to older (average age 15 years) individuals (Tranulis et al. 2021). In theory, the transmission of prions from decaying carcasses can contaminate the environment and, in turn, infect new individuals, even when no prion shedding is detected in the lymphatic tissue. Current epidemiological knowledge supports the idea that sporadic CWD found in old moose is not contagious among live animals (EFSA Panel on Biological Hazards (BIOHAZ) et al. 2023). Evidence from red deer is limited to three cases, but old age (only one case was aged) and the lack of detection in the lymph nodes with standard diagnostic tools are similar to those found in moose. In-depth overviews of the characteristics of sporadic and contagious CWD are given elsewhere (Tranulis et al. 2021), and we focus on the rest of the review mainly on the contagious CWD strain so far only detected in reindeer.

New CWD strain in reindeer

Origin

The origin of the CWD strain in Norway remains unclear. Initially, it was assumed that the pathogen came from the USA or Canada (Benestad et al. 2016), similar to exports from the USA to Canada and further to South Korea (Kim et al. 2005). Due to the novelty of strains (above), it is 'unlikely' or 'very unlikely' that CWD in northern Europe stems from recent transatlantic transfers of CWD from the USA or Canada (Table 1). Laymen argued that CWD in Norway might have originated from scrapie in sheep. This is 'unlikely' or 'very unlikely' based on the observed differences between classical and atypical/Nor98 scrapie prions and the reindeer CWD agent (above) and the lack of previous evidence of scrapie spillover to cervids in Europe. No signs of lymphoid or gastrointestinal accumulation of abnormal prion proteins were observed in sheep that had grazed in CWD-infected ranges in Nordfjella (Harpaz et al. 2022). It has also been suggested that the origin may represent a novel emergence in reindeer

(Mysterud et al. 2020d), but this remains to be documented and can be considered 'likely'. We have discussed the possibility of strain evolution in the Discussion section.

Contagiousness

The detection of prions in the lymph nodes of all 21 Norwegian reindeer that tested positive for CWD strongly suggests that the disease is contagious, although no study has been conducted to directly establish that prions are shed in saliva and other bodily fluids, as found in North American CWD. Epidemiological evidence consistent with contagiousness has been confirmed in Nordfjella, with 19 cases clustered in this population (Mysterud et al. 2019a). Hence, we are 'almost certain' that this CWD variant is contagious under natural conditions.

Pathogenesis

There is limited information on the pathogenesis of the new CWD strain in reindeer (Table 1). The few observations are consistent with the 2–3-year period from infection to death observed in white-tailed deer and mule deer (Johnson et al. 2011). We consider the duration of the clinical period of weeks to two months more uncertain ('about as likely as not') for the CWD strain in reindeer in Norway. We assumed that animals that reach the clinical stages of the disease under harsh winter conditions succumb more rapidly than during summer. The first detected reindeer (3–4 years old) died under stress related to a helicopter following the herd during capture for GPS marking. The prolonged preclinical phase, which is characteristic of prion diseases, makes subclinical infections highly relevant. It is unknown whether disease progression in some animals remains 'arrested' for prolonged periods in a preclinical stage, with prions localized only in peripheral lymphoid tissue (carriers). We consider it 'almost certain' that the lethality of fully developed and uninterrupted clinical prion disease is 100%. There was one observation of an assumed clinically sick reindeer (photographed), but no other reindeer infected with CWD showed clinical signs of the disease after the index case. The duration from infection to death and the expression of clinical signs differed for reindeer infected with prions from white-tailed deer and elk in the USA (Mitchell et al. 2012).

Demographic pattern

No calves, one male yearling, six adult females, and 12 adult males were detected with CWD infection in Nordfjella, Norway. Adult males had a 2.7 times higher probability of being infected than adult females (Mysterud et al. 2019a), but with wide 95% credible intervals [1.0–7.2]. The likelihood of CWD infection increased with age in males. All patterns were consistent with the demographic patterns documented in mule deer and white-tailed deer (Miller and Conner 2005, Samuel and Storm 2016), whereas elk had similar age patterns but more equal infections among the sexes. The age pattern of CWD infection in reindeer is more certain ('almost certain') than the sex differences ('very likely', Table 1).

Table 2. An overview of process uncertainties related to the epidemiology of CWD in wild reindeer in Norway. Scale of uncertainty according to EFSA (methods).

Characteristic	Predicted pattern	Observation Norway	Status 2023 (references)
Transmission routes	Direct and indirect/ environmental, early stages predominantly direct transmission	Demographic pattern consistent with direct transmission	Likely
	Environmental persistence of prions sufficient to cause re-infection	Detection of prions in soils near salt licks	About as likely as not (after ≥ 5 year fallowing) (www.nrk.no/vestland/nye-funn-problematisk-for-villreinen-1.15701470)
Epidemiology	Slow initial growth (decade), then more rapid, population decline late stage (depending on management)	Not long enough time to measure	Very likely
	Spatial spread, lower prevalence in new population	Detection in new population (Hardangervidda)	Almost certain
Spillover – cervids	Occur among cervid species with susceptible *PRNP*; mule deer, white-tailed deer, elk, moose	Not observed; cervidized mice susceptible to new strain	Very likely (Pritzkow et al. 2022)
Zoonotic potential	No cases observed in humans, various evidence indicate very low zoonotic potential	Not observed; humanized mice indicate very low zoonotic potential	Very unlikely (Pritzkow et al. 2022), review (Tranulis and Tryland 2023)

Susceptibility (PRNP)

The *PRNP* gene encodes the prion protein, and nucleotide variation in the *PRNP* leading to amino acid substitutions in the prion protein can profoundly affect the susceptibility to prion disease. Breeding in robust *PRNP*-variants has been successfully utilized for breeding to control classical scrapie in sheep and goats. Similarly, CWD susceptibility in white-tailed deer, mule deer, and elk differs depending on the *PRNP* gene (Moazami-Goudarzi et al. 2021). Investigation of *PRNP* variation among the 19 CWD-positive reindeer in Nordfjella showed that two variants of the *PRNP* gene (alleles), the 'wild-type' ('A') allele, common to most cervids and an octapeptide 'deletion' allele ('C') were overrepresented among the CWD-positive animals compared to that in 101 CWD negative reindeer. In contrast, animals carrying *PRNP* alleles 'B' (Ser225Tyr), 'D' (Asn176Asp), and 'E' (Val2Met-Gly129Ser-Val169Met) were less frequent among CWD-positive animals, showing that these *PRNP* alleles reduced CWD susceptibility (Güere et al. 2020). Different genotypes of *PRNP* determine the susceptibility to different strains of prion disease (Mead et al. 2019). Whether animals that carry two copies of *PRNP* alleles 225Y, 176D, and 2M129S169M as homozygous or in combination are robustly protected from CWD is considered 'as about as likely as not'.

Transmission routes and environmental persistence

Currently, we do not have direct knowledge of the relative roles of direct and indirect (environmental) transmission routes. The demographic pattern of CWD infection in reindeer was similar to that in the US and Canada, suggesting the same transmission mechanisms in the assumed early epidemic stages (Mysterud et al. 2019a). Knowledge of the environmental persistence of prions in the relevant soil types and climates in Norway is limited (Kuznetsova et al. 2023).

Epidemiological pattern and impact on the population

The rates of epidemic growth, geographic spread, and population impact of CWD on reindeer remain unknown. This is due to the combination of a short time since detection and rapid removal of the infected population in Nordfjella. Due to the presence of the *PRNP* 'wt' allele in sympatric red deer, moose, and roe deer, it is likely that the new CWD strain can infect these species, a notion supported by in vitro studies (Pritzkow et al. 2022, Harpaz et al. 2023). To date, spillover to other cervids has not been detected. We consider the role of predation or scavenging in CWD epidemiology beyond the scope of this review.

Measurement uncertainty

Measurement uncertainty was primarily related to the occurrence of CWD at first detection, estimation of prevalence at detection, or establishment of the likelihood of CWD absence in a population (Table 3). From 2012 to 2015, CWD surveillance occurred across Europe due to fear of spillover after the 'mad cow epidemic'. There were only seven samples from wild reindeer (Tranulis et al. 2021). However, Europe was considered free of CWD.

What have we learned?

Hunter harvest surveillances are conducted in 24 wild reindeer areas (Fig. 3) and in selected areas with moose and red deer, while roe deer are primarily monitored based on road kills (Rolandsen et al. 2022). We now know with high certainty that contagious CWD is not widespread and that its prevalence is very low in areas where it might occur (Mysterud et al. 2023b). The 95% credible intervals provided in the estimation of the prevalence and probability of freedom from CWD explicitly quantify the uncertainty 'within the model'. The assumptions regarding test sensitivity over the duration of infection in different tissues (lymph nodes and brain) still rely on the aspects listed in Table 2; however, the estimates are not very sensitive to variations in these assumptions (Viljugrein et al. 2019).

Estimation of the prevalence of CWD

At the beginning of the depopulation in Nordfjella, four confirmed cases were identified after the index case. The estimated number of infected individuals was in the range of 5–52, whereas the observed number was 14 additional cases of CWD after complete depopulation by May 2018 (Mysterud et al. 2019a). In contrast, after the detection of a single case of CWD in a new area, Hardangervidda, the estimated prevalence was approximately 0.1% (95% credible interval 0–0.6%, Mysterud et al. 2023b). For a population of 5000–6000 reindeer, there is high uncertainty regarding the absolute number of infected individuals. Having 0 or 10–20 infected individuals represents two different management situations that cannot be separated using the current estimation.

Table 3. An overview of measurement uncertainties related to the status of occurrence of CWD in wild reindeer populations in Norway.

Characteristic	Observations Norway – Status 2023	References
More detections in same population upon first detection	19 cases in Nordfjella 2016–2018	Mysterud et al. (2019a)
	2 cases on Hardangervidda 2020, 2022	
Prevalence	Nordfjella: adult males 1.6% [1.4–1.8%], adult females 0.5 [0.5–0.7%][1]	Mysterud et al. (2019a)
	Hardangervidda: ~ 0.1% [0–0.6%][1]	Mysterud et al. (2023b)
Probability freedom-of-CWD	Explicitly quantified uncertainties[1] at various design prevalences in all other 22 populations (after harvest 2021)	Mysterud et al. (2023b)

[1]The 95% credible intervals provide explicitly quantified 'within-model' uncertainty. Assumptions regarding test sensitivity over the duration of infection in different tissues (lymph nodes and brain) still rely on the aspects listed in Table 2, and process uncertainty will not be included in the 95% credible intervals.

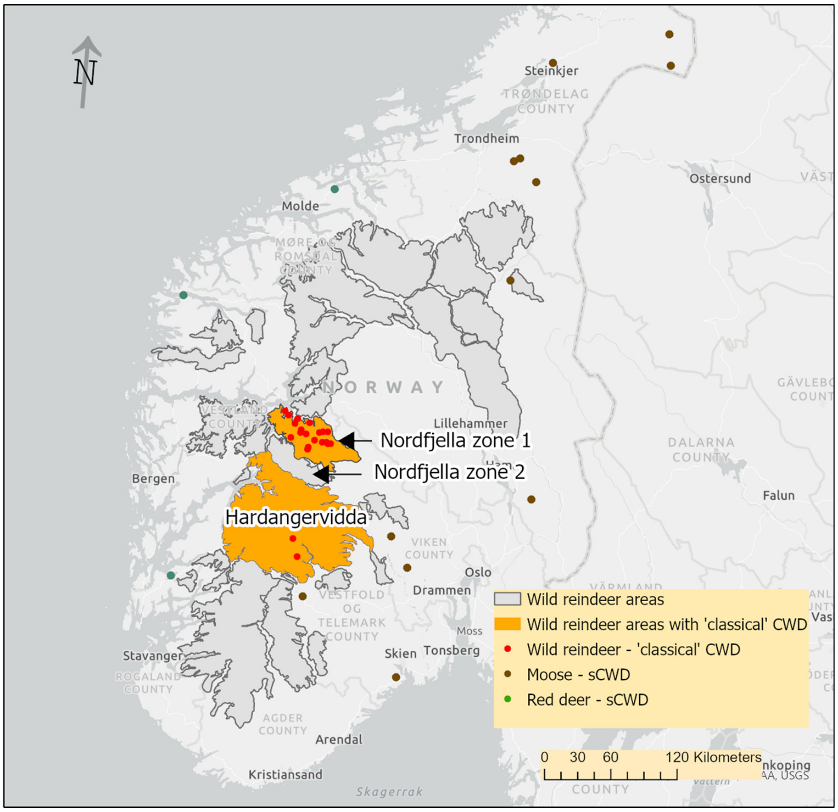

Figure 3. An overview of the 24 reindeer management areas and all cases of CWD recorded in Norway until 1 October 2023. Note that cases in moose and red deer are sporadic and likely not contagious variants of CWD.

Probability of CWD freedom

Determining the absolute absence of CWD in a population is impossible when relying on postmortem tissue testing. Therefore, the probability of freedom is calculated relative to a given level of infection, which is termed the design prevalence. A high probability of freedom from CWD was only obtained for a prevalence of 1% in areas with large populations (Mysterud et al. 2023b). For areas close to known CWD cases, management authorities have chosen a design prevalence of only four individuals (Mysterud et al. 2020a), and most populations without detection have only 60–85% certainty of CWD being absent at such a potentially low prevalence.

Environmental uncertainty and stochasticity

Environmental uncertainty is intrinsic to any ecosystem or management scenario. An important issue is how environmental conditions combine with demographic stochasticity and other factors to induce random variations in epidemic growth (Williams and Brown 2016). Not all CWD introductions result in outbreaks because transmission and mortality are stochastic processes (Belsare et al. 2021, Hanley et al. 2022). With a very low initial number of infected individuals, all infected individuals may die by chance before passing the pathogen to another. In simulations, many disease introductions die out owing to stochasticity in the initial epidemic stages, but only if the critical mass of infected individuals is below ~ 5 and typically within five years of introduction (Belsare et al. 2021). The likelihood of death increases with heavy harvesting. This possibility is relevant for planning culling in areas with a recent introduction of CWD but may also lead to a false hope of CWD eradication without depopulation. Other chance events had an impact on the CWD situation in Norway. For example, the winter of 2017/2018 had unusually early snow, which made culling by marksmen based on snowmobiles more successful than anticipated (Mysterud et al. 2019b).

Implementation uncertainty

Implementation uncertainty is related to 1) sociopolitical acceptance and compliance at relevant levels of management (governance), 2) the effectiveness of implemented control measures, and 3) the identification and evaluation of unintended (positive or negative) side effects. Management actions involve culling or intensified harvesting (Table 4), and less intrusive actions such as surveillance (Section 'Measurement uncertainty'), zonation, ban on feeding, perimeter fencing, and saltlick hotspot fencing (Table 5).

Governance

A major uncertainty is whether one can implement actions in a socio-ecological system, that is, the translation of policy into practice (Tyre and Michaels 2011, Nuno et al. 2014), which is a key issue for CWD management (Decker et al. 2006). Although experts typically highlight the value of prompt intervention, such actions are sometimes met with skepticism from the unprepared public. The first response to the detection of CWD in Wisconsin, USA, was a decline in harvest despite increased quotas due to hunters not hunting (Heberlein 2004).

The main finding in Norway is that recreational hunting has been moderately effective and has not reached harvest targets for reindeer (Mysterud et al. 2019b) and even less so for moose and red deer (Mysterud et al. 2023a). How this may be related to the hunters' ability and/or willingness to complete quotas is uncertain. Another challenge of governance for reindeer is whether the political system risks the social conflicts inherent in culling strategies. The Norwegian Environment Agency has addressed issues of the social (and local) acceptance of governance by establishing working groups of scientists and local stakeholders for both Nordfjella (regarding reintroduction) and Hardangervidda (regarding harvesting management). These initiatives have been well-received by most local stakeholders. We discuss this in more depth later ('Reindeer CWD culling timeline').

Other minor management actions were implemented without much debate. A suboptimal route for perimeter fences was chosen because of resistance from sheep farmers with grazing rights in the area, who argued that the fences negatively affected area usage (Mysterud et al. 2022). A legal regulation for feeding cervids was introduced, but an interview survey suggested that this was only weakly complied with outside the CWD zones (Mysterud et al. 2019c).

Effectiveness

A considerable amount of experience in the management of prion diseases in Europe comes from the history of scrapie in sheep and goats and BSE in cattle. Efforts to combat these diseases have been highly successful, and many of the principles are grounded in the TSE regulation of the EU (European Parliament and Council 2001). The most important actions include limiting the movement of livestock between areas (no trade and implementation of zonation), isolation of infected herds (fencing and herding), depopulation (and subsequent fallowing and restocking), contact tracing to other herds, and breeding robust *PRNP*-genotypes.

These management principles have been successful in a range of prion strains and livestock host species. However, there are challenges to implementing these principles for CWD of wild cervids. It is difficult to fully depopulate an area, limit natural cervid movement between areas, and isolate infected populations that often inhabit forested areas lacking clear population boundaries. There is little direct scientific evidence on the quantitative efficacy of various management practices to limit CWD, including zonation, perimeter fencing, salt lick fencing, and the ban on supplementary winter feeding of cervids (an overview of evidence from Norway is presented in Table 5).

Considerable evidence suggests that breeding a more robust *PRNP* combats prion diseases in livestock effectively. An EFSA report summarizing efforts to control classical scrapie highlighted that eradication strategies must include *PRNP* genetic data (EFSA Panel-on Biological Hazards (BIOHAZ) 2014). However, the extent to which *PRNP*-informed breeding can be used to control CWD in wild reindeer remains unclear. The introduction of more 'robust' and *PRNP* genotyped reindeer bulls into populations would decrease susceptibility, particularly for small populations, and if combined with the removal of other males. Robust *PRNP* genotypes are present at low frequencies in wild reindeer populations investigated to date (Güere et al. 2022), and such breeding is probably unrealistic in most cases. A strategy using semi-domestic reindeer to enhance CWD resilience is practically more feasible owing to both ease of handling and selection and a higher prevalence of robust *PRNP*-genotypes in semi-domestic reindeer. This breeding raises ethical and conservation issues if applied to wild reindeer.

Table 4. Implementation uncertainties – part 1: Harvesting and culling operations aimed to control CWD.

Management action and rationale	Implementation	Effectiveness	Side effects	References
Host culling of reindeer to de-populate	Hunters, Nordfjella 2017	Limited in effectiveness in removal of CWD infected hosts	Some extra host movement, but not recorded to new unit	Mysterud et al. (2019b)
	Marksmen, Nordfjella population 2017/2018	Highly effective removal of CWD infected hosts		Mysterud et al. (2020b)
Host culling of reindeer for proactive surveillance (90% freedom in 1 yr, 99% after 5 yrs)	Hunters, Nordfjella Zone 2 2018	Did not reach targets	Not assessed	
	Marksmen, Nordfjella Zone 2 2019	Effective, but more time consuming than for zone 1	Not assessed	
	Hunters, Hardangervidda 2019	Highly effective	Not assessed	Mysterud et al. (2021c)
Host culling of reindeer to limit CWD	Hunters, Hardangervidda 2020–2022. Target of 1500 females and adult males down to 0–3%	Moderately effective, did not reach targets	Not assessed	
Host culling of moose and red deer to lower risk of spillover	Hunters, Nordfjella 2016–2021	Not effective, far from reaching targets	Not assessed	Mysterud et al. (2023a)

Table 5. Implementation uncertainties – part 2: management actions other than culling and surveillance aimed to control CWD.

Management action	Implementation and rationale	Effectiveness	Side effects	References
Zonation	Nordfjella and Hardangervidda, limit export of contagious material	Uncertain, not assessed. Carcasses in Nordfjella were arrested until negative CWD test	Extra effort for hunters and costs of containment. Not assessed	
	Selbu (after detection of sCWD in two moose)	Proved unnecessary, as sCWD not contagious	Not assessed	
Perimeter fencing in Nordfjella	Limit reindeer movement into Zone 1, from Zone 2 and Filefjell	Partly effective, some crossings, snows down	Not assessed	Mysterud et al. (2022)
Salt lick fencing in Nordfjella and Hardangervidda	Limit access of cervids to potential environmental pathogen reservoirs	Red deer and reindeer enter through the opening intended for sheep	Not assessed	Mysterud and Rolandsen (2019)
Fragmentation and border surveillance	Limit reindeer movement from infected populations	Not assessed	Not assessed	Mysterud et al. (2020c)
Ban on supplemental feeding of cervids	Some feedings continue despite ban	Reduced clustering of red deer when deep snow	No broader ranging behavior detected	Mysterud et al. (2019b, c)

Eradication of CWD (through depopulation)

Attempts to eradicate CWD among wild white-tailed deer by increasing harvesting have been made after detection in Wisconsin and Minnesota but have not been successful. In Wisconsin, part of this was due to the inability to increase the harvest through ordinary hunting and a lack of social acceptance (Heberlein 2004), but probably also due to late detection. Minnesota started early surveillance and aimed to 'act aggressively to eliminate the disease, if possible' (Department of Natural Resources 2019), but was still unsuccessful. A common denominator may be late detection after the introduction of CWD in an area when relying on testing of the hunter harvest only, and CWD is well established upon detection (Belsare et al. 2021). It appears difficult to fully depopulate forested areas without clear population boundaries or to fallow areas with a flux of immigrating deer due to lower density (and potential for reinfection from environmental prions).

In the USA and Canada, geographical spread has been due to natural host movement and the movement of infected hosts in the extensive deer farming industry. Depopulation and five-year fallowing have been applied to manage CWD among farmed deer and elk in fenced areas (Department of Natural Resources 2019), but systematic evidence of success rates has not been published.

Limitation of CWD through harvesting

Experiences from the USA and Canada suggest that limitation, rather than eradication, is a realistic outcome for forest-dwelling cervids. In the USA, spatially targeted harvesting (i.e. increased harvest around CWD detection) of white-tailed deer (Manjerovic et al. 2014, Hedman et al. 2020) and male-biased harvesting of mule deer (Miller et al. 2020, Conner et al. 2021) are effective in limiting CWD.

What have we learned?

Depopulation of Nordfjella Zone 1 was effective in removing all animals, likely because the reindeer in Norway inhabit fragmented areas of mostly open alpine landscapes. Perimeter fences were installed between Nordfjella Zones 1 and 2 to limit reindeer movement into Zone 1 during the following period. Perimeter fences have aided in maintaining areas free of reindeer, although semi-domestic reindeer occasionally cross fences (Mysterud et al. 2022). There have been attempts to herd the borders between wild reindeer populations (Mysterud et al. 2020c) without documentation of whether they have been effective in limiting host movement. To date, depopulation has not been considered in the recent detection of CWD in Hardangervidda, Norway. Owing to the nomadic behavior of reindeer within each population, spatially targeted harvesting is not applicable; male-biased harvesting in Hardangervidda is currently applied for effective surveillance and to limit CWD but with unknown efficacy for reindeer.

Side effects

Host culling can cause both known and unintended side effects. The host culling to combat CWD killed thousands of reindeer, and it is partly responsible for the fact that wild reindeer was listed as 'Near Threatened' on the Red List of Species in Norway for the first time in 2021 (Artsdatabanken 2021). If the population size is sufficiently reduced by culling, it can affect the genetic diversity (Flagstad et al. 2022). In general, management has not paid much attention to the potential adverse side effects beyond the reduction in population size. Marked demographic changes after male-biased harvesting may affect calving times (Mysterud et al. 2002), but there have been limited direct efforts to measure the potential unintended side effects. The seasonal movement of reindeer during host culling by hunters and marksmen has been assessed in Nordfjella (Mysterud et al. 2020b). Increased movements were observed during the late winter with ongoing marksmen culling, but none of the GPS-marked reindeer moved to a new epidemiological unit. There was no evidence of longer or larger home ranges of red deer after feeding bans (Mysterud et al. 2021b).

Discussion

The broad-scale spreading of CWD among cervids in North America is a tragedy one aims to avoid in Europe. There was considerable knowledge about CWD in North America and experience with the management of prion disease in livestock in Europe when CWD was first detected in Norway in 2016 (VKM et al. 2017). CWD management in Norway faces uncertainties that can be grouped into four categories. A new strain of CWD may potentially have different disease characteristics and epidemiology (process uncertainty), there is virtually no previous CWD surveillance (measurement uncertainty), and environmental variation may combine with demographic stochasticity to induce random variation in epidemic growth (environmental uncertainty). Finally, management actions can be difficult to implement, their (quantitative) effects are uncertain, and they may have unintended side effects (implementation uncertainty). Our identification of key uncertainties related to the management of CWD may aid future management and distribution of funding for research and surveillance.

New knowledge of two main types of CWD

Science aimed at lowering process-related uncertainties has mainly been researcher-initiated and not followed by an organized plan at the national level (Supporting information). In general, prior knowledge of CWD and other prion diseases has proven to be highly relevant for the new situation with the emergence of CWD in Norway. A major discovery was the assumed cases of sporadic CWD (sCWD) cases in moose (Pirisinu et al. 2018) and red deer (Vikøren et al. 2019). Based on the knowledge of sporadic prion diseases in other ruminants, sCWD was assumed to be less contagious due to the lack of prion detection in lymph nodes (an indication of prion shedding and hence contagiousness) (Sola et al. 2023). However, CWD zonation and intensified surveillance were established around the first cases of sCWD in moose in Selbu, Norway, in 2016. Accumulating evidence suggests that sCWD is not likely to be contagious. Intensified surveillance of sCWD cases in Norway ended from 2021 onwards (EFSA Panel on Biological Hazards (BIOHAZ) et al. 2023), while continued surveillance in the municipality where sCWD was first found (with three detected cases) was based on a precautionary principle. Therefore, 'classical' and contagious CWD and sCWD now involve very different management policies owing to epidemiological differences (Mysterud et al. 2021a).

Currently, there is no indication that the new CWD strain in reindeer is qualitatively different from CWD in North American cervids. However, the pattern of prion shedding, duration from infection to death, and duration of the period with clinical signs remain uncertain. A project is now being funded to conduct challenge experiments with the new CWD strain in captive reindeer, which will reduce process uncertainty. However, the quantitative details of the pathogenesis are not considered key uncertainties, as these details are unlikely to affect how a contagious variant of CWD should be treated.

Process uncertainties key to reindeer reintroduction to Nordfjella

Possible environmental sources of CWD prions are an important uncertainty that was highlighted (VKM et al. 2018) and a critical uncertainty for the scheduled re-establishment of reindeer into the depopulated range of Nordfjella Zone 1 following a minimum of five-year fallowing (The Norwegian Food Safety Authority and The Norwegian Environment Agency 2017). The level of protection of *PRNP* genotypes lacking alleles 'wt' or 'deletion' remains a key uncertainty facing the possibility of environmental contamination. The novel *PRNP* allele 2M129S169M included a substitution at codon 129 (G/S). Mutations in a neighboring position are known to markedly lower susceptibility in humans (Asante et al. 2015), but whether genotypes homozygous for the allele 2M129S169M are robust to CWD is currently unknown and is considered 'about as likely as not' (Table 1). Due to the lower prevalence of highly susceptible 'wt' alleles in semi-domestic reindeer (Güere et al. 2022) and the ease of handling and selection, using semi-domestic stock has arisen as an option for re-establishment. Veterinary experts favor this alternative, whereas conservation biologists favor using reindeer with wild traits despite their higher susceptibility to CWD (Köller et al. 2022b). The lack of knowledge regarding the presence of an environmental reservoir of prions of epidemiological relevance in Nordfjella Zone 1, whether robust *PRNP* is required to eliminate CWD, and the level of protection of *PRNP* genotypes appear to be the most critical process uncertainties remaining in the management of CWD in Norway.

Measurement uncertainty is critical to culling in Hardangervidda

Extended surveillance was implemented to reduce measurement uncertainty after the first animal with CWD was detected, and the occurrence of CWD was highlighted as a key uncertainty in 2016 (VKM et al. 2016). CWD surveillance has been successful in obtaining large sample sizes covering a wide geographical area. Despite this, the occurrence of CWD remains a major uncertainty in the current management of Hardangervidda and its adjacent populations (Fig. 3). The effects of a given management action depend on the occurrence of CWD in other areas. The depopulation of reindeer in Nordfjella did not eradicate CWD from Norway, as CWD was already present but was not detected in another population (Hardangervidda). Establishing freedom from infection in populations adjacent to one with CWD detection takes time, with surveillance relying on harvested animals. CWD was detected in Hardangervidda on 3 September 2020 after 3500 samples tested negative. Similarly, CWD was detected in only one population (Hardangervidda); however, there is a lack of certainty regarding the absence of CWD in adjacent reindeer areas. Estimation and detection problems at low prevalence appear to be inherent features of CWD epidemiology (Belsare et al. 2021). We will not obtain a full overview of the occurrence before making critical decisions, and delaying actions will increase the risk of further spread. Early action or even preemptive culling is required to eradicate CWD (Belsare et al. 2021). This dilemma will be at the core of management decisions in 2023 for reindeer in Hardangervidda and its surrounding areas.

Aims and implementation uncertainties along the reindeer CWD culling timeline

At the first detection of CWD in Nordfjella (2016), the objective was to scientifically evaluate management strategies; however, it was not specific as to whether the objective was to limit or eradicate CWD (VKM et al. 2017). The hope was to try to eradicate CWD from Norway or at least halt the ongoing epidemic when depopulation was carried out in Nordfjella Zone 1. The eradication of CWD in Norway appears to be the goal up to the point of detection of CWD in Hardangervidda. The management objective then became explicitly given as to 'limit, if possible eradicate' CWD (VKM et al. 2021). However, actions to limit versus eradicate differ markedly, given the current situation ('effectiveness' above). Therefore, we can separate the two main phases of CWD management: after detection in Nordfjella and after detection in the reindeer management area of Hardangervidda (Fig. 2).

The Nordfjella phase (2016–2019). In this 'acute' phase, political ambitions were high and aimed at eradicating contagious CWD in reindeer. The Norwegian Food Safety Authority and Norwegian Environment Agency agreed on a common strategy based on scientific opinions issued by the Norwegian Scientific Committee for Food and Environment, addressing a number of questions raised by the two governmental bodies. Culling by marksmen in Nordfjella Zone 1 mainly caused local resistance. After depopulation, the Norwegian Food Safety Authority asked for increased surveillance in the adjacent Nordfjella Zone 2 and the Hardangervidda populations to increase surveillance depth to enable early detection or to achieve 'freedom-from-CWD' status (Mysterud et al. 2020a). In the small population of Nordfjella Zone 2, some additional culling by marksmen (52 reindeer) was carried out in the winter of 2018. In the large population of Hardangervidda, there was good collaboration with local reindeer management at this stage to markedly increase the harvest in 2019 to achieve this goal.

The Hardangervidda phase (2020–now). The CWD situation markedly changed when cases were detected in the much larger reindeer population in Hardangervidda in September 2020 and September 2022. The 8000 km^2 area includes local landowners and activists with a high societal impact and political influence at the national level. The locals now feared the same depopulation as in Nordfjella Zone 1. The Norwegian Scientific Committee for Food and Environment issued a report in January 2021 suggesting the removal of most adult males (down to 0–3%; 'weak limitation') or population reduction down to 'minimum viable population size' without causing loss of genetic variation ('strong limitation') (VKM et al. 2021). The Norwegian Food Safety Authority and Norwegian Environment Agency subsequently (April 2021) provided the Ministry of Agriculture and Food and Ministry of Climate and Environment with recommendations on how to handle CWD in Norway. The two directorates did not fully agree on the extent of the population reduction and how quickly adult males should be removed. The Norwegian Food Safety Authority favored a rapid implementation of the strategy, employing many of the tools used in the Nordfjella Zone 1 depopulation (marksmen, snowmobiles, and helicopters), while the Norwegian Environment Agency argued that ordinary hunting should be the main tool to achieve these goals and to postpone winter culling by marksmen, thus aligning with hunter and landowner interests and other local stakeholders.

This appears to be the first turning point, signifying an important change in Norwegian CWD management, with more emphasis on socio-political acceptance and considering the negative long-term consequences of conflicts with local stakeholders. In 2021, the same occurred after the hunting season with no new CWD detection. Representatives from the local management threatened not to organize a hunt in the fall of 2022 if culling by the marksmen was carried out during the winter of 2022. Managing this population of approximately 6000 reindeer is difficult without the help and support of local management. The Norwegian Environment Agency continued its explicit argument not to upset the local management when stopping winter culling. Subsequently, both the Norwegian Environment Agency and Norwegian Food Safety Authority jointly advised against the extraordinary culling of wild reindeer in Hardangervidda during the winter and spring of 2022 (23 November 2021), and the Ministry of Agriculture and Food and Ministry of Climate and Environment concluded accordingly (11 February 2022).

The Norwegian Environment Agency initiated a one-year dialogue process between scientists and local management (Fig. 2), which was merged into an advisory working group. Overall, the group reached similar conclusions as the Norwegian Scientific Committee for Food and Environment, aiming to drastically reduce the number of adult males but with a differing view regarding the target size of the female population (sufficiently large to produce 1500 calves each year) (Köller et al. 2022a). This goal was set for cultural and economic reasons, as the local management considers this the minimum population size required to manage the population through recreational hunting (a major issue for local stakeholders). This involved democratically elected local representatives of both landowners ('Villreinutvalg') and the politically appointed local management group ('Villreinnemnd'). Most local representatives agree with this conclusion. However, when harvest quotas were not reached by recreational hunting in the fall of 2022, the planned culling of adult males by marksmen in Hardangervidda winter of 2023 instigated fierce debates. A video of a reindeer wounded from a helicopter in Nordfjella during the culling was leaked to the press, and the day after, the Ministry of Agriculture and Food and the Ministry of Climate and Environment issued a joint press release stating that winter culling would not be effectuated (press release 8 December 2022), thus setting aside both the current advice from the Norwegian Scientific Committee for Food and Environment, the report from the one-year dialogue process between scientists and local management, and advice from both the Norwegian Environment Agency and the Norwegian Food Safety Authority, to carry out removal of adult males by marksmen culling during winter of 2022/2023. We consider this as the second turning point in Norway's CWD control strategy.

Conclusions

The management of CWD in Norway has not followed an explicit adaptive management protocol but has changed practice when new evidence has arisen. Positive news seven years after detection of CWD in Norway: Epidemiological evidence shows that sCWD does not appear contagious among moose (and probably red deer) under natural conditions and that the management policy has changed accordingly. The most critical process uncertainty remaining for reindeer management is the uncertain epidemiological consequences of potential environmental reservoirs of prions in the depopulated Nordfjella Zone 1 and whether the elimination of CWD is realistic without actively using *PRNP* genetics. Intensive surveillance has lowered measurement uncertainty. Contagious CWD has not been detected in moose, red deer, or roe deer, and we now know that contagious CWD is not widespread among reindeer. The main setback and game changer was that CWD was detected in a new population of reindeer inhabiting the Hardangervidda area. However, intensive surveillance cannot eliminate critical measurement uncertainty in the early stages of CWD epidemics. Hence, critical decisions regarding culling and depopulation must be made despite the uncertain occurrence of CWD. Governance now appears to be a key uncertainty in Norwegian CWD management, with ministries ignoring advice from their own management institutions. These management institutions have given their advice based on a political aim of 'limiting, and if possible, eradicate CWD'. Political decisions are now more in line with limiting CWD. The eradication of CWD appears unlikely with current efforts, and there is no clear long-term plan for managing CWD with the aim of limiting it. It is beyond the scope of this review to document how management has tackled the uncertainties and risk management decisions. However, our review provides a baseline for conducting in-depth interviews with stakeholders on how they have tackled the challenging trade-offs between short- and long-term aims.

A potential game-changing factor would be a shift in the assessment of the zoonotic potential of CWD. Currently, it is regarded to be 'very unlikely' that CWD is zoonotic (Waddell et al. 2018, Tranulis and Tryland 2023), but some findings leave room for concern (Hannaoui et al. 2022). Detailed studies are required to characterize the potential for zoonotic transmission of the new CWD strains. Initial reports suggested that the zoonotic potential of North European CWD strains is comparable to or even lower than that of North American CWD strains (Pritzkow et al. 2022, Wadsworth et al. 2022). A growing field of research is the extent to which prion strains can evolve (Huor et al. 2019, Sun and Telling 2023); 'prions are themselves capable of a form of evolution, in which changes in their structure that impact their rate of growth or fragmentation are replicated, making such changes subject to natural selection' (Acevedo and Stewart 2023). In transmission experiments, strains can become contagious (Bian et al. 2021). Human exposure will continue if CWD is not eradicated, and repeated exposure is an inherent risk factor for developing new strains, which may (or may not) be more zoonotic than the original strain (Silva 2022).

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Author contributions

Atle Mysterud: Conceptualization (lead); Writing – original draft (equal); **Michael A. Tranulis:** Conceptualization (supporting); Writing – review and editing (equal). **Olav Strand:** Writing – review and editing (equal). **Christer M. Rolandsen:** Writing – review and editing (equal).

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Supporting information

The Supporting information associated with this article is available with the online version.

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