Chronic wasting disease — A prion disease through a One Health lens

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Prion diseases or transmissible spongiform encephalopathies (TSEs) are consistently fatal and transmissible neurodegenerative diseases that affect various mammals, including humans. The most prominent examples are scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, chronic wasting disease (CWD) in cervids, and Creutzfeldt-Jakob disease (CJD) in humans (1). These diseases are caused by prions, unconventional infectious agents that consist only of protein and replicate without using DNA or RNA as an information carrier. Instead, prions arise from a conformational conversion of the host-expressed cellular prion protein (PrP^{C}) into the infectious isoform PrP^{Sc}, which is prone to aggregate and eventually cause neurodegeneration in the brain (2). Histologically, prion diseases are characterized by spongiosis, astrogliosis, and accumulation of PrP^{Sc} in the brain. There are various etiologies, including sporadic occurrence (the most common form in humans, but also discussed for CWD in European moose), genetic origins upon specific germline mutations in the gene encoding the prion protein, and disease acquired by infection (1).

Chronic wasting disease was observed for the first time 1967 in a captive deer facility in Colorado and classified as a TSE in the early 1980s (3). It is characterized by a prolonged (years) preclinical stage, with clinical signs that include weight loss, hypersalivation, polydipsia, polyuria, ataxia, and behavioral changes (e.g., separation from the herd). Many infected animals die before reaching the terminal clinical stage, as they are predisposed to other diseases (e.g., pneumonia), predation, or roadkill (4).

To date, CWD has been detected in 28 US states, 4 Canadian provinces, South Korea, and the North European countries of Norway, Finland, and Sweden. It naturally affects mule deer *(Odocoileus hemionus)*, white-tailed deer *(O. virginianus)*, elk *(Cervus canadensis)*, red deer *(C. elaphus)*, and moose *(Alces alces)* in North America and in addition, reindeer *(Rangifer tarandus tarandus)* in Europe (5,6). It is the only prion disease known to affect wild and captive animals and considered the most contagious prion disease. It is efficiently transmitted directly and indirectly between animals, facilitated by widespread distribution of infectious prions in peripheral tissues e.g., skeletal muscle, and shedding of prions in saliva, urine, and feces (6). Shedding starts during the preclinical stage and contaminates the environment. Since prions are very resistant to degradation, they persist in the environment and remain infectious for many years (7). Transmission of CWD among and between cervid species is modulated by species-specific polymorphisms in the prion protein gene that translate into single amino acid substitutions in PrP^{C}. These polymorphisms, e.g., M132L in elk, S225F in mule deer, G96S in white-tailed deer, or S138N in reindeer, can significantly prolong the incubation period of CWD (6). Even though this might offer a certain level of protection, a better understanding of shedding by these animals is required to determine whether prolonged incubation periods are beneficial, as this may cause prolonged prion shedding. Furthermore, distinct strains of CWD prions can arise in cervids with such polymorphisms. Such strains are thought to consist of PrP^{Sc} conformers and can have a different host range (8), increasing the potential of transmission to non-cervid species.

Altogether, the continuous geographic spread of CWD, the annually increasing prevalence and the lack of widely acceptable management strategies (particularly in wild cervids) raise several questions: How does CWD affect cervid populations? What is the impact of CWD on human health and communities? Are there new approaches to manage and mitigate CWD transmission and spread? These questions imply that there is a strong interrelation among animal, environmental, and human health — making CWD a prime example of a One Health issue.

Impact on cervid populations

Chronic wasting disease is a silent killer that cannot be recognized until the clinical stage of disease, which lasts only for several months. The infectious agent consists only of protein, with the same primary structure as the host-expressed PrP^{C}. These properties impose challenges for confirming CWD infection, as polymerase chain reaction (PCR) or serological assays generally used for diagnosis of infectious diseases cannot be used for CWD. Diagnosis of CWD relies on detection of PrP^{Sc} in brain or lymphatic tissue, generally recovered post-mortem. Non-invasive, ante-mortem assays are very limited, hampering surveillance in wild cervids, which mostly rely on hunters submitting heads of harvested animals. Therefore, CWD can spread unrecognized and reach quite high prevalence — more than 40% in the most endemic areas in Colorado and Wyoming where CWD was initially detected (9,10). In Saskatchewan, the

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province with the first cases of CWD in wild deer in 2000, the prevalence among male mule deer in the south Saskatchewan River valley is > 80% (11). In Alberta, where CWD in wild deer was first reported in 2005, prevalence in male mule deer is > 50% in southeastern parts of the province (12).

Several studies were done, mostly in the US (Colorado and Wyoming) to determine impacts of CWD on cervid populations on monitoring prevalence and population size. Higher survival estimates for non-infected compared to CWD-positive mule deer were reported from Wyoming, also projecting a population decline at an infection rate of 27% in females, resulting in an estimated annual population decline of 21% under current CWD prevalence (9). White-tailed deer in Wyoming were 4.5 times more likely to die annually than CWD-negative deer, and a 10.4% annual decline was projected (10). A study in Colorado monitored uninfected and infected adult mule deer for a 2-year interval, during which 53% of infected deer died, whereas 83% of uninfected deer survived (13). The authors estimated the average life expectancy of an infected deer to be only an additional 1.6 y, compared to an additional 5.2 y for uninfected deer (13). Overall, these studies demonstrated that CWD reduced survival of individual animals and caused deer populations to decline.

The CWD spillover to endangered woodland caribou *(Rangifer tarandus caribou)* is of great concern. They have the same PrP^C primary structure as white-tailed and mule deer, and experimental as well as natural transmission to reindeer suggests that there is no transmission barrier to caribou (5,14). In Alberta and Saskatchewan, CWD is spreading northwards. In Saskatchewan, there are CWD-positive white-tailed deer near or overlapping woodland caribou habitats. Woodland and barren-ground caribou in western Canada carry the minor S138N encoding allele that is considered protective; however, the population in Saskatchewan at highest risk for CWD is among those with a low frequency of that allele (15). Whereas contracting CWD might be detrimental for these already declining populations, woodland caribou in Saskatchewan are in contact with the more northern, migratory barren-ground caribou *(Rangifer tarandus groenlandicus)*. These interactions could open the gateway to the Arctic for CWD, with barren-ground caribou distributing infectious prions while migrating.

Zoonotic potential and impact on public health

The potential for zoonotic transmission of prion diseases has been exemplified by BSE, which gave rise to a new form of human prion disease, termed variant Creutzfeldt-Jakob disease (vCJD; 16). Worldwide, 239 cases of vCJD have been reported, including 2 in Canada (16).

The zoonotic transmission of CWD is an ongoing concern, with an estimated 7000 to 15 000 CWD-infected cervids consumed annually in North America. Health Canada recommends to not eat meat from CWD-positive animals, whereas studies addressing zoonotic potential have yielded conflicting data. Epidemiological studies in CWD endemic areas have neither indicated an increased incidence of CJD patients, nor unusual prion disease subtypes (17). Several studies assessing the zoonotic potential of CWD, both *in vitro* and *in vivo*, concluded that the risk of CWD crossing the transmission barrier to humans was low, but cannot be excluded (18). Most notably, squirrel monkeys were susceptible to intracerebral and oral CWD infection, whereas *Cynomolgus* macaques, considered the most relevant non-human primate model for zoonotic prion transmission, were not (19); however, a more recent Canadian-led study suggests that CWD is transmissible to *Cynomologus* macaques upon oral or intracerebral infection (19).

Despite no solid proof that CWD is or is not transmissible to humans and the ongoing spread of the disease, it already impacts communities in several ways. Most importantly, hunting families, especially Indigenous communities in whom cervids have a key role in health, food security, and cultural expression, are at risk for zoonotic transmission. Farmers experience economic losses due to export restrictions for cervid products, but also for crops and hay from CWD-endemic regions. Declining cervid populations due to CWD as projected will mean fewer deer and elk to hunt, with repercussions on tourism and outfitting, and further negative implications on food security for Indigenous communities.

Chronic wasting disease management — A mandate for One Health

Currently, CWD management options especially in wild cervids are restricted to targeted culling of cervids, most drastically used in Norway, where an entire reindeer herd of ~2000 animals was removed by sharp shooters in an attempt to contain CWD. Depopulation of farms is still the main management strategy for farmed cervids, along with voluntary enrollment into the CWD Herd Certification Program established by the Canadian Food Inspection Agency (CFIA). This program builds on strict surveillance, annual status progression of the farm, and regulating movements of animals between farms such that a farm can only bring in new cervids from another enrolled farm with a similar or higher certification status. In return, these farms are eligible for destruction of the herd and compensation, if CWD is detected.

In wild cervids, management is even more complex. Recent promising findings on potential vaccines for CWD (20,21) and natural compounds for environmental remediation (22) may provide novel tools to mitigate CWD spread, but additional research is needed to validate these results in natural CWD hosts and real-world settings. It is also important to note that a comprehensive, multi-pronged approach will be necessary to reduce CWD transmission and spread. Such a strategy would include measures to protect cervids from infection (e.g., through vaccination or selecting for genotypes associated with reduced CWD susceptibility), and to remediate prions in hotspots in the environment. The first priority for protection measures should be populations close to CWD endemic areas that are not yet affected, e.g., woodland caribou. Since cervids do not recognize provincial borders, a successful CWD management plan needs a coordinated, interprovincial, pan-Canadian effort to be successful. Furthermore, the needs and perspectives of the various stakeholders affected by CWD should be considered — e.g., Indigenous communities, wildlife managers and veterinarians,

hunters and farmers, to ensure that management strategies are applied in a culturally acceptable way and do not further interfere with lives and livelihoods of humans dependent on cervids. For developing successful management tools and strategies, an interdisciplinary approach, bringing together basic scientists, wildlife veterinarians and managers, wildlife biologists, human health experts, policy analysts, and agricultural economists, is inevitable. With this inclusive approach and effective tools in place, it will be possible in the longer term to reduce the spread of CWD, preserve healthy cervid populations, protect endangered caribou, and mitigate risks of CWD to human health, food safety, and food security.

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