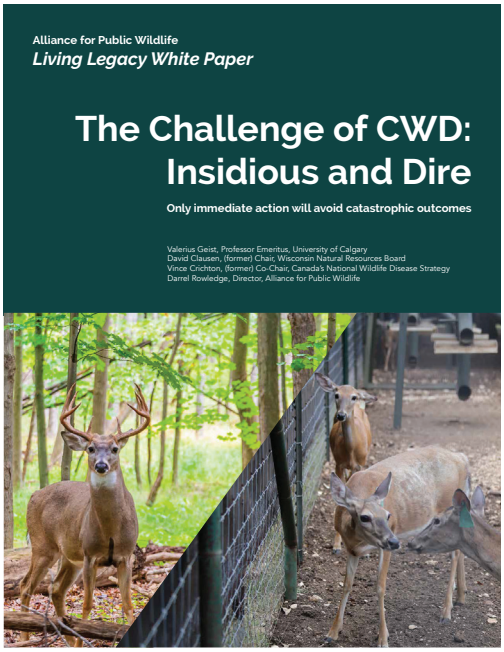
October 2017, Update

Chronic Wasting Disease: Insidious, Dire, and URGENT

Late-breaking research reinforces the need for urgent action



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Shortly after the release of The Challenge of CWD: Insidious and Dire, key findings in several areas of CWD research alerted prion scientists and authorities around the world to the urgency of the current situation. Careful scrutiny, repetition, and thorough interdisciplinary analyses are needed—but the implications are profound.

To supplement the existing analysis, this update summarizes some of those findings, the potential implications and inferences, and considers the role of policy, protocol, and prudent response.

After extensive consultation, the addition of **"URGENT"** to our title reflects the consensus of leading experts and stakeholders from every sector. The new findings and insights only amplify the demand for the immediate emergency-level responses outlined previously.

Unfortunately, official responses to increase testing of harvested deer, and some official but obscure warnings about the importance of keeping *"agents of all known prion diseases from entering the human food chain"* are inadequate: They fail to address primary causal and exacerbating factors perpetuating the epidemic.

Delay in containing the spread of and exposure to infectious diseases (especially one as contagious and persistent as CWD), increases risk, compromises options for effective response, raises costs of implementation, and diminishes efficacy of those measures. Yet decisions regarding containment of CWD—and the role of private, commercial interests—continue to be subverted by false presumptions, flawed policy, and compromised processes that violate fundamental principles of science and ethics.

Public trust and the precautionary principle impose a duty of care on government to authorize and require objective analysis, and to anticipate and avoid worst case outcomes. This obligation is especially critical regarding the influence of public policy, where political or short term budget factors must not be allowed to interfere or prevent comprehensive analysis, or adequate response to new data.

Recent developments and new findings

January 2017 The European Food Safety Authority (EFSA) Scientific Panel on Biological Hazards, released "Scientific opinion on chronic wasting disease (CWD) in cervids."[1] EFSA emphasized a precautionary approach, stating: *"There is no evidence of an absolute species barrier between CWD-affected cervids and humans." "CWD prions are present in the skeletal muscle and other edible tissues, so humans may consume infected material in enzootic areas."*[2]

Advocating prevention and containment, EFSA advised they would *"recommend, if necessary, additional animal health risk-based measures to prevent the introduction of CWD into the EU cervid populations and to prevent its spread within the EU."* Potential means of importation cited include live animals, carcasses, velvet antler, urine based products, mineral or lick blocks, silage and feed harvested or produced using plants originating in counties where CWD has been detected, within Norway and abroad. EFSA will be updating this assessment regularly

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to accommodate new data or identification of new risk factors.[3]

March 29, 2017 Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards report entitled: "CWD in Norway — A state of emergency for the future of cervids (Phase II)"[4]

The analysis describes CWD as highly contagious, fatal, persistent, with severe population impacts, and evolving risk factors. The Panel outlines a precautionary and proactive approach to prevent, control, and eradicate CWD. Citing North America's experience, they outline the necessity of aggressive measures to prevent its introduction by restricting movement of *"live animals, products and any material that can carry the infective agent,"*[5] and to effect immediate eradication measures to avoid irreversible harm. The Panel advises that these prevention, control, and eradication measures and all risk factors are to be continually assessed.

May 25, 2017 Edinburgh Scotland, Prion 2017 Conference: Dr. Stefanie Czub, (Canadian Food Inspection Agency) reported efficient oral transfer of CWD to cynomolgus macaques—the closest non-human primates allowed in research.[6] Of particular significance regarding zoonotic risk, 2 of 3 were infected from ingesting CWD+ pre-clinical white tailed deer meat (muscle); they were fed 200 grams per month over a period of two years, representing a total of 5kg.[7] This is equivalent to consuming 7 oz of meat (a small steak or a couple of burgers) per month—a level that is regularly and substantially exceeded by hunter families per week.

Recent research confirms macaques are susceptible to CWD, including from ingestion of CWD+ meat.

Of the three macaques on that diet, two were proven infected and showed clinical symptoms (ataxia, apathy, anxiety, tremors, and wasting). One was euthanized after losing 1/3 of her body weight in under six months. Additionally, 1 of 2 challenged orally with 10g WTD brain homogenate (dosed five times with 2g) was infected. Thus of 5 macaques challenged orally, 3 are positive to date. Additionally, 2 of 6 macaques challenged intracranially (IC - steel wire method) were also infected. Results for the method considered as baseline, or proof of concept (IC injection of brain homogenate), are negative (0 of 2; one remains alive 8 years PI).

May 25, 2017 Edinburgh Scotland, Prion 2017 Conference: Dr. Alastair Ward, Senior Lecturer at the University of Hull, UK Research Director for the Deer Initiative reviewed search data for papers and reports with the term "Prions."[8] 468,423 results matched that criterion. Those addressing CWD (the largest, most infectious, and fastest growing biomass of prions in world history) numbered only 1322,[9] or less than 1/2 of one percent. Searched by "potential management to control spread" that number fell to 11,[10] i.e., less than one percent of the minuscule number of CWD papers. His search showed only 2 papers addressing "Consequences of CWD for other species or the environment."

After noting significant CWD impacts now being documented in North American cevids, Ward noted that 55 of the world's 92 species of cervids are listed on World Conservation Union's "Red List" i.e., facing endangerment.[11] He then cited four international conservation treaties to which most of the affected areas are signatories. These include: Convention on Biological Diversity (CBD), the United Nations Sustainability Development Goal, CITES, and the EU Habitat Directive.[12]

Developing insights in pathogenesis of TSEs

The precise mechanisms of molecular prion templating and cellular amplification of TSEs are not fully known, but key insights are emerging. At the molecular level, biophysicists advise that the amyloid state of prion protein is not the infective or 'templating' state. Instead, conversion is driven by "an unstable intermediate precursor." "Once in the final amyloid state, the back transition to the infectious precursor is a rare event, precisely because amyloid is so stable."[13] This is consistent with demonstrated persistence and proteolytic resistance, and reduces the need to explain sufficient templating capacity of PrP^{d} bound as amyloid.

Investigations of the cellular mechanisms and pathways of propagation and spread of prions are providing better comprehension and potential opportunities for therapeutic intervention. In May, 2017 research by C.E. Hoover et al. examined the "Pathways of Prion Spread during Early Chronic Wasting Disease in Deer"[14] confirming that CWD followed the pattern of scrapie[15] rather than exclusive central nervous system prion replication observed in bovine spongiform encephalopathy (BSE).

As with scrapie, where early and distinct phases of replication and amplification occur in secondary lymphoid organs[16] the "pathways" documented in white tailed deer through four months "show CWD uptake occurs in the oropharynx with initial prion replication in the draining oropharyngeal lymphoid tissues, rapidly followed by dissemination to systemic lymphoid tissues without evidence of neuroinvasion. These data highlight the two phases of CWD infection: a robust prion amplification in systemic lymphoid tissues prior to neuroinvasion and

establishment of a carrier state."[17]

July, 2017 Greenlee et al. (USDA)[18] reported "Experimental transmission of the chronic wasting disease agent to swine after oral or intracranial inoculation." Because risk of exposure to CWD for both domestic and feral pigs is significant, these large populations present potential reservoirs of infection, amplification, or passage.

"In the US, feeding of ruminant by-products to ruminants is prohibited, but feeding of ruminant materials to swine, mink, and poultry still occurs. Therefore, it is possible that, if a CWD-affected cervid carcass entered the food chain through a commercial slaughter house, domesticated farmed and pet swine could be exposed to CWD infectivity in commercially prepared rations. As of 2015, feral pigs have been reported in 39 US states and in 12 of these states CWD has been detected in free-ranging cervid populations. Environmental contamination with CWD infectivity in excreta or decomposing carcasses contributes to horizontal transmission of CWD in mule deer. Prion infectivity has been shown to persist on the surface of contaminated plant leaves and roots and in soil. Therefore, feral pigs could be exposed to infectivity through scavenging of CWD-affected carcasses, consumption of contaminated vegetation, and while rooting around in the soil during foraging."[19]

Positive results in orally inoculated pigs suggest that it may be possible for swine (domestic or feral) to serve as a reservoir for prion disease under natural conditions.

To assess disease, amplification, and passage risk for these populations, Greenlee et al. "challenged domestic swine with the chronic wasting disease agent by inoculation directly into the brain (intracranially) or by oral gavage (orally). Disease-associated prion protein (PrP^{sc}) was detected in brain and lymphoid tissues from intracranially and orally inoculated pigs as early as 8 months of age (6 months post-inoculation). Only one pig developed clinical neurologic signs suggestive of prion disease." "The amount of PrP^{sc} in the brains and lymphoid tissues of positive pigs was small," … and further bioassay showed "low attack rates in Tg002 mice" suggesting "that there is a relatively strong species barrier to CWD prions in pigs." "Regardless, positive results in orally inoculated pigs suggest that it may be possible for swine to serve as a reservoir for prion disease under natural conditions."[20]

While it appears (for the strains of CWD tested) pigs may fall into the category of non-adaptive prion amplification (NAPA),[21] the reservoir and amplification risks of CWD in pigs are significant. Very large populations of domestics may present opportunities for both amplification and repeated passages to ecosystems, as well as risk of human exposure. With very high reproductive rates, wide climate and diet tolerance, and the ability to root through or under fences, feral swine have been described as among the most destructive invasive species in North America. Extensive overlap of CWD-infected areas and significant exposure of these omnivores to infected carcasses or other CWD contamination presents formidable challenges, uncertain, evolving, and potentially severe risks to wild ecosystems and economies, to agricultural economies, and potentially to human health.

Discussion

The recent laboratory findings are significant and troubling, elevating risk profiles with direct, associated, and multiplier effects. In immediate practical terms, increased potential of transfer to humans requires greater and more urgent precautionary measures. The necessary responses and costs extend to associated economies and their networks; and as evident in the increasing global scrutiny, these threats extend to wildlife, ecosystems, economies, and people around the world. Further, and as has been repeatedly documented, the implications necessarily extend to global trade, where pathogen-based trade barriers can carry enormous costs.

At the base level, integrating the scientific findings and insights may suggest helpful inferences regarding baseline presumptions and bench standards. For example, infective capacity of inocula and source tissues have been predicated on biochemical assessment of PrP^{res}. Yet, and accepting the phenomenal density and dynamic

complexity of cellular proteins, if molecular re-templating is driven in significant part by an intermediate precursor, to the extent that titers of PrP^{res} reveal PrP^{d} bound as amyloid rather than the intermediate precursor state, perhaps the presumptions of infectivity based on PrP^{res} are not entirely accurate.

There is no questioning the infectivity of brain tissue, and these processes are complicated by sheer brute force numbers; but perhaps brain inoculum is not as disproportionately infectious as has been long presumed. The role of an intermediate precursor state may be among the factors that help explain the many instances, across prion strains and species, where PrP^{res} levels have failed to fully correlate with expected infectivity.[22]

Amplification Pathways

Confirmation of prion amplification in lymphoid tissues prior to neuroinvasion explains why lymph nodes provide better and earlier detection than obex in deer. But these amplifying pathways may also offer insights explaining divergence from baseline expectations as occurred in the macaque research. Perhaps the "baseline, proof of concept challenge" of direct intracranial injection of brain homogenate may not be as disproportionately severe as has been presumed.

The (n) is far too small for any grand extrapolations, but it is consistent with the comparable oral infectivity of meat (2 of 3) vs (1 of 2) consumption of brain in these macaques. More pointedly, it seems almost necessary to explain why simply eating modest portions of CWD+ meat from preclinical deer presented greater risk (2 of 3) than homogenized PrP^{cwd} brain matter—even when directly injected into the test animal's brain (0 of 2).

Whatever the explanation, the prospect of eating meat posing greater or even comparable risk of transferring CWD to a person than direct IC challenge, certainly raises questions about the wisdom of allowing hunter families to continue to consume thousands of CWD-infected animals every year.

The macaque results are from an ongoing study and were reported May 23, 2017, but all of the positive results were confirmed in 2015. This level of science is certainly non-trivial, and would require great rigour and cautious review—especially of unexpected results with significant implications. Delay in releasing results, however, does not preclude advancing preparatory measures to secure vital precautionary measures; and these findings were not unexpected.

They join a body of substantial and compelling evidence indicating that zoonotic risk of CWD is far from negligible; and known prevalence and harvest data suggest some 7,000—15,000 CWD-infected animals are consumed by hunter families every year. These macaque data were cited in an internal Risk Advisory Opinion from Health Canada dated April 26, 2017,[23] but it has still not been released to the public. It advised that *"CWD has the potential to infect humans,"* and then reiterated the WHO's 2012 position that *"No tissue that is likely to contain (TSE) agent, nor part or product of any animal which has shown signs of a TSE should enter the (human or animal) food chain."*[24]

Similarly, August 17, 2017 the U.S. Centers for Disease Control and Prevention updated the risk advisory on their website to note that *"animal studies suggest CWD poses a risk to some types of non-human primates, like monkeys, that eat meat from CWD-infected animals or come in contact with brain or body fluids from infected deer or elk. These studies raise concerns that there may also be a risk to people."*[25] They then note the WHO recommendation in place since 1997.[26]

Feral Macaques & CWD

Among the dozens of exotic species in Texas, there are hundreds of old world primates in a large area enclosure, and feral populations of macaques have also been observed. The Born Free USA Primate Sanctuary located on 186 acres near San Antonio, Texas is a permanent home to more than 600 macaques, vervets, and baboons.[27]

While this must be kept in perspective (as a precautionary reminder), CWD has been confirmed in multiple white tailed deer near Hondo in Medina County, less than 50 miles (generally upstream) from the primate sanctuary; and there may be feral macaques closer. Various predators and scavengers including many species of birds (known to passage CWD in feces), as well as thousands of feral hogs may serve as vectors. Concentrations of CWD along riparian areas has been well documented, and waterborne transfer is certainly possible.

Impacts

CWD infected deer, feral macaques, and feral pigs are currently sharing the same landscape in Texas.

Complete, comprehensive, multi-disciplinary analysis of these issues and developments is essential. But extensive

consultation with leading experts and stakeholders confirms a consensus that recent findings only amplify the demand for vital responses outlined previously. Further, the approach and official responses announced to date are so obviously inadequate that not a single scientist, expert, or objective authority expressed confidence that current measures could possibly contain or mitigate the CWD epidemic.

Indeed, consensus is that the announced responses—and the approach that produced them—will continue to avoid and exacerbate the problems. Any budget savings (of inaction) will be vastly surpassed by costs of continuing to allow the spread, evolution, and increased exposure to the disease, while dramatically increasing the likelihood of worst case outcomes.

Chronic Wasting Disease: Insidious, Dire, and URGENT

The CWD crisis is insidious, dire, and URGENT—requiring immediate, emergency-level response. We must secure mandate and funding to:

1. Contain the geographic spread and exposure to CWD by enacting and enforcing an immediate ban on the movement of all live cervids, all potentially CWD-infected carcasses, animal parts, products, exposed equipment, trailers, or other sources of infectious materials.

2. Mandate and implement for hunters, convenient, cost-free, rapid testing of all animals harvested from CWD-affected areas.

3. Ensure that no CWD-infected material reaches the food or feed chains, and that it is instead properly disposed of.

4. Establish and fund accountable research and science-based policy to protect public interest (health, wildlife and related industries, agriculture, First Nations Treaties, our economies and communities).

Outlining details and the need-specific terms of those broad measures requires comprehensive expert analyses and vital stakeholder participation. But it is equally clear that we must identify and avoid the systemic flaws that enabled and exacerbated this crisis, and that continue to disallow our ability to correct course—more than 15 years after the U.S. Secretary of Agriculture officially declared CWD a "State of Emergency."[28]

That every major factor has only gotten worse is not the fault of our scientists or the civil service. It is virtually impossible to 'science' a way out of a policy and process problem. To attempt to do so while disallowing or dissuading critique of the flawed policy, and while invoking terms of reference that violate fundamental tenets of science… is absurd.

This goes beyond simple "regulatory capture"[29] to what might be called "imposed compromise of scientific or ethical principles." It is an egregious violation of the public trust doctrine, the precautionary principle, and it abuses the professionalism of our trusted experts.

Forcing layers of arbitrary boundaries on efforts to address dynamic, interrelated processes is not just unfair, it is often seriously counterproductive. The resulting positions and official statements are invariably couched in authoritative and scientific language—but in reality, the vague and mostly aspirational terms can be grossly misleading. This can not only misrepresent the seriousness and urgency of a crisis and the (in)adequacy of official responses, it can replace that dire reality with a false sense of security.

It sets up a classic catch-22:

> *Legislators are precluded from changing the policy or approach without clear judgments of need, that will only come from comprehensive assessment—that is precluded by the false presumptions and parameters of the existing policy.*

Our leaders aspire to good governance—that requires objective, informed input from all relevant disciplines and experts. The pleas of our experts are clear and unequivocal, but largely off the record: They support and will engage objective, comprehensive analysis, but it must be initiated and supported by governments. It should be accompanied with an unequivocal directive to ensure that our experts, vital stakeholders, and the public not only have a right to challenge flawed policy, we have a responsibility to do so.

The developments and increasing risk factors of CWD have global implications. These challenges are massive and will not be short lived. We must, absolutely, confront the uncertain risks and potential consequences; and we must implement vital measures to avoid worst case outcomes.

But we should also recognize that protein diseases are among the greatest remaining challenges in biology, and we have few treatments for any of them. Overlap and crossover opportunities are very significant, and we must expand basic research rather than have it shortchanged as opportunity cost. Our comprehensive analysis must confront and contain the CWD crisis, but with care, we can identify and enable opportunities for advancing public benefit.

Endnotes

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"I should much regret to see grow up in this country a system of large private game-preserves kept for the enjoyment of the very rich. One of the chief attractions of the life of the wilderness is its rugged and stalwart democracy; there every man stands for what he actually is and can show himself to be."

~ Theodore Roosevelt, 1893

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