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## Reinterpreting Chronic Wasting Disease Emergence in the USA in Light of Historical Surveillance Limitations

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ABSTRACT: We estimated the probabilities of detecting one or more chronic wasting disease (CWD) cases  $(P_{det})$  in free-ranging cervids in the continental US during 1997-2001. Based on sample sizes reported by respective state authorities at the time and a target for detectable apparent prevalence (i.e., a design prevalence) of 0.001 (one positive per 1,000 animals statewide), estimated  $P_{det}$ were <50% for 39/46 states where CWD had not been detected in the wild prior to 1997 and were <5% in 20/26 states located east of the Mississippi River. The survey designs and sample sizes reported by most states prior to 2002 would have yielded exceedingly small detection probabilities for focal CWD outbreaks. Although most CWD foci in the US were first detected in 2002 or after, the data presented here and elsewhere suggest it is plausible that an unknown number of these—some established perhaps decades earlier—were already present but had simply eluded detection. These data highlight uncertainty regarding timelines for CWD emergence in the US. Accepting—and to the extent possible quantifying—uncertainty in the historical distribution of CWD throughout the US seems a necessary foundation for better understanding its emergence, its drivers and patterns of spread, and its response to various interventions—past, present,

Key words: Chronic wasting disease, cervid, CWD, detection probability, prion, surveillance.

The transmissible spongiform encephalopathy chronic wasting disease (CWD; Williams and Young 1980) affects North American deer (Odocoileus spp.) and wapiti (Cervus canadensis), as well as related cervid species on at least three continents. First described in the western US, this prion disease has been diagnosed in captive and free-ranging deer and wapiti since the late 1970s (Williams and Young 1992). As of mid-2024, the cumulative known distribution of CWD in North America includes most US states and multiple Canadian provinces. Some popular articles and scientific publications have alluded to CWD's "rapid spread" since the early 2000s (e.g., Escobar et al. 2020; Center for

Infectious Disease Research & Policy 2024; Robbins 2024). This interpretation seems based on the following facts taken on face value: CWD cases had been reported in 12 North American jurisdictions as of mid-2002 (Williams et al. 2002), whereas the number with reported cases has tripled since then.

The accepted storyline for CWD's emergence tends to overlook the influence that uneven surveillance effort over time and across jurisdictions has probably had on observed patterns (Miller and Fischer 2016). Considerable uncertainty surrounds the origin(s), epidemiological relationships, and start times of many, perhaps most, CWD outbreaks (Williams and Young 1992; Wasserberg et al. 2009; Miller and Wolfe 2023). The possibility that CWD emerged independently more than once in North America cannot be discounted given the open question of its origin(s). It seems clear from published accounts that people were moving CWD-exposed captive cervids extensively by the 1970s-1980s (Williams and Young 1992; Temple et al. 2001; Williams et al. 2002). Yet organized surveillance for CWD in either captive or free-ranging settings was not undertaken outside of Wyoming and Colorado, US, until the late 1990s and occurred mostly in states west of the Mississippi River before 2002 (Temple et al. 1998, 2001; Evans et al. 2014; Thompson et al. 2023). Here we summarize state-reported CWD surveillance data from free-ranging cervids sampled during 1997 – 2002 and estimate associated detection probabilities. Our purpose is not to criticize past efforts during a period of lower capacity, fewer resources, and less understanding of the longterm impacts of CWD, but rather to highlight the uncertainty regarding the true timeline(s) for CWD emergence in the US.

For several years beginning in the late 1990s, the Southeastern Cooperative Wildlife Disease Study (SCWDS; University of Georgia, Athens, Georgia, US) queried state wildlife management agencies across the US about their CWD surveillance activities and sample sizes as part of an annual hemorrhagic disease surveillance questionnaire. We reviewed the compiled data from 48 reporting states in the continental US and subdivided them based on geographic region and known risk level (Supplementary Material Table S1). The Mississippi River delineated western (including Minnesota and Louisiana) and eastern states to reflect a perceived historical boundary to CWD distribution in the US. States were further subdivided based on known CWD occurrence or perceived risk of prior CWD introduction and establishment at two time points, 1997 or mid-2002 prior to the 2002-03 hunting season, as follows: "endemic" states already had detected CWD in the wild; "exposed" states had detected infected captive cervids within the state; "border" states shared a border with an endemic state; the remainder had no known risk at the time. We placed states with multiple sources of risk in the highest applicable category (endemic>exposed>border). The temporal break point that we chose for comparison separated the years immediately before and just after a large influx of federal funding became available in 2002 to support CWD surveillance nationwide, albeit unevenly distributed. Based on states' reporting, most samples were from free-ranging, hunter-harvested cervids, mainly deer (Odocoileus spp.). Lacking additional details on individual submissions, we assumed each sample had an equal infection probability and thus that each contributed equally to the overall probability of detecting CWD regardless of species, demographic group, and submission circumstances.

We summed data reported by each state from 1997 – 2001 and compared these to data from 2002, assigning states to a risk group based on what was known about CWD distribution and states' perceived risk in the US as of 1997 or as of mid-2002. State identities have been anonymized for reporting. For each state where CWD was not known to be endemic at each time period's start, we calculated the probability of detecting one or more CWD

cases  $(P_{det})$  based on the number of samples reported (n) as (Cannon and Roe 1982):

$$P_{det} \sim 1 - (1 - prev)^n, \tag{1}$$

where the target for detectable apparent prevalence (prev) was set at 0.001, a relatively high prevalence for an early-stage outbreak in an area the size of an entire state. This approach assumes an infinite population and spatially random distributions of disease occurrence and sampling and therefore probably overestimates the true probability of detecting cases within a state where CWD is not already widely distributed (Joly et al. 2009).

The total numbers of cervids screened for CWD during 1997 – 2001 offered detection probabilities ("confidence"; %) of <50% for 39/46 states included where CWD had not already been detected in the wild (Fig. 1A). West of the Mississippi River—where CWD had been detected well before 1997—sampling tended to be higher in states where perceived risk was greatest. East of the Mississippi River, detection probabilities were <5% in 20/26 states before 2002. Surveillance in the one eastern state that detected CWD before mid-2002 achieved a detection probability of approximately 65%; prevalence estimated from statewide sampling during 1999 - 2001 was 0.003 (three positives among 1,102 samples screened; Joly et al. 2003), and subsequent surveillance revealed that CWD was well established at the time of its detection (Joly et al. 2009). Detection of a similarly expansive focus before 2002 would have been improbable ( $P_{det} < 5\%$ ) in at least 15 states.

Multiple states disclosed newly detected CWD cases and locations in the wild or in captivity during 2000 to mid-2002 (Fig. 1A; Williams et al. 2002). This motivated a marked increase in US federal funding to help support states' surveillance nationwide beginning in fall 2002. Sample sizes increased for most states beginning in fall 2002 (Figs. 1B and 2), but detection probabilities still varied widely and the tendency remained for more sampling in states where perceived risk was greatest (Fig. 1B). Additional detections followed (Fig. 1B; Evans et al. 2014; Thompson et al. 2023). Surveillance

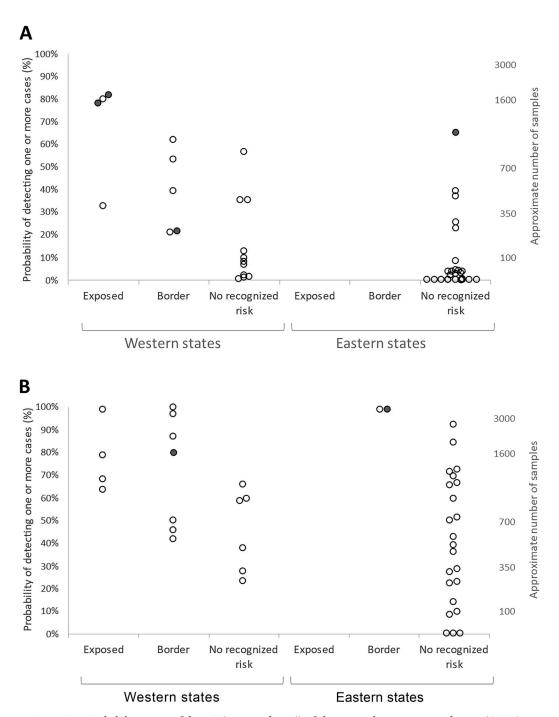


FIGURE 1. Probability or "confidence" (expressed as %) of detecting chronic wasting disease (CWD) at a state-level design prevalence of 1 in 1,000 (0.001) during (A) 1997-2001 or (B) 2002. Points represent the respective detection probabilities (expressed as %) calculated from the total number of free-ranging cervid samples screened for CWD in the contiguous states of the USA in each time period as reported by state wildlife management agencies in states where CWD had not been detected in the wild as of 1997 (n=46 states) or 1997 (n=46 states). Each state's data were pooled for 1997-2001. For purposes of comparison, the Mississippi River was used to delineate western (including Minnesota and Louisiana) and eastern states. States were further subdivided based on the known CWD occurrence or perceived risk (prior to 1997 for panel A or

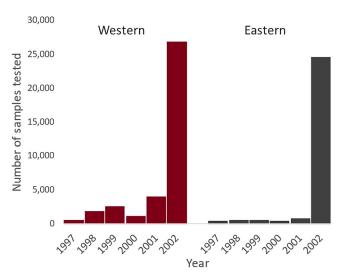


FIGURE 2. Total numbers of free-ranging cervids sampled and tested for detecting chronic wasting disease (CWD) annually across the "western" and "eastern" continental USA during 1997-2002, illustrating regional differences and the sharp rise in sampling in 2002. Bars are the sums of cervid samples screened for CWD each year as reported by state wildlife management agencies in states where CWD had not been detected in the wild as of  $1997~(n=46~{\rm states})$  or mid- $2002~(n=42~{\rm states})$ . For purposes of comparison, the Mississippi River was used to delineate western (including Minnesota and Louisiana) and eastern states. Most samples were collected from hunter-harvested cervids, mainly deer ( $Odocoileus~{\rm spp.}$ ). See Supplementary Material Table S1 for sample count data.

efforts since 2002 have varied widely among states and over time, probably influenced by the availability of federal funding and regional or local diagnostic support, as well as by local, regional, and national interest and concern (Evans et al. 2014; Miller and Fischer 2016; Thompson et al. 2023). Approaches for designing and conducting CWD surveillance have been refined over time (e.g., Miller et al. 2000; Samuel et al. 2003; Joly et al. 2009; Evans et al. 2014; Jennelle et al. 2018; Clement et al. 2023; EFSA Panel on Biological Hazards [BIOHAZ] 2023). Where implemented, these refinements also may have facilitated CWD detection in recent decades.

Newly emergent CWD outbreaks in freeranging cervids are difficult to detect—even with today's understanding and tools because of their focal nature and the relative scarcity of infected animals (Samuel et al. 2003; Joly et al. 2009; EFSA Panel on Biological Hazards [BIOHAZ] 2023). It follows that lags between the start of an outbreak and its detection seem far more likely than not and should be expected (Miller and Fischer 2016). The survey designs and sample sizes reported by most states prior to 2002 (Fig. 1 and Table S1) would have yielded exceedingly small detection probabilities for focal CWD outbreaks. In the absence of additional epidemiological data, the uncertainty inherent in historical surveillance sensitivity limits the ability to reliably distinguish outbreaks where CWD may have been introduced and spread relatively rapidly (e.g., via human activities), from outbreaks where the disease was introduced some time ago but remained undetected.

2002 for panel B): CWD already had been detected in captive cervids (exposed), shared border with a state where CWD already had been detected in the wild (border), or no recognized risk at the time. States with multiple sources of risk were counted in the most direct risk category that applied (exposed > border). Solid (black) circles denote states that detected one or more CWD cases in the wild during the time period. Most samples were collected from hunter-harvested cervids, mainly deer (Odocoileus spp.). See Supplementary Material Table S1 for sample count data.

Interpreting and reporting a survey that fails to detect CWD as unqualified "evidence of absence" seems misinformed, then or now. Rather, such surveillance outcomes are more accurately reported in terms of what the upper limits of undetectable prevalence might be within the sampled population or geographic area and time frame represented (e.g., Cannon and Roe 1982; EFSA Panel on Biological Hazards [BIOHAZ] 2023). This approach is akin to assessing the "long-run risk" for rare adverse effects (Hanley and Lippman-Hand 1983). If cases are eventually detected, then historical data combined with estimates of the apparent prevalence and the geographic extent of the outbreak at the time of detection may provide further insights for estimating the duration and plausible range of timelines for emergence (e.g., Miller et al. 2000; Joly et al. 2009; Wasserberg et al. 2009; Thompson et al. 2023). The combination of historical and contemporary surveillance information is critical when wildlife managers are evaluating effectiveness of preventive management, determining management goals, and deciding whether aggressive actions (e.g., localized population reduction) are justified following the first detection of CWD in an area.

The management consequences of misinterpreting "zero numerator" surveillance data include over- or underappreciation of potential exposure source(s), as well as misinformed assessments of risk factors, epidemic growth, and efforts to prevent or contain CWD (Miller and Fischer 2016). We therefore encourage states that have not already done so to reexamine their extant CWD surveillance data in terms of the extent to which CWD could have been present but as yet undetected over time using appropriate spatial subdivisions and timeframes, as demonstrated elsewhere (e.g., Joly et al. 2009; EFSA Panel on Biological Hazards [BIOHAZ] 2023). Doing so would provide a far more complete picture of what is and is not known about CWD distribution in the US than that currently available.

Although most CWD foci in the US were first detected in 2002 or after, the data presented here and elsewhere suggest it is plausible that an unknown number of these

foci-some established perhaps decades earlier-were already present but had previously eluded detection (Wasserberg et al. 2009; Miller and Fischer 2016; Thompson et al. 2023). It follows that little if any surveillance before 1997, compounded by uneven efforts since then, have contributed to potential (mis)perception and misrepresentation of CWD's rapid expansion in the last two decades. Accepting—and to the extent possible quantifying uncertainty in the historical distribution of CWD throughout the US seems a necessary foundation for better understanding its emergence, its drivers and patterns of spread, and its response to various interventions—past, present, and future.

We acknowledge the thousands of cervid hunters and others nationwide who participated in these early efforts to survey for CWD in the US. We thank state wildlife management agencies for sharing data on sampling efforts to detect CWD during 1997 – 2002, and thank V. F. Nettles for having the foresight to gather and assemble these data at the time. Funding that supported individual state efforts included respective states' cash funds and well as Federal Aid in Wildlife Restoration funds and cooperative agreements from the US Department of Agriculture-Animal Plant Health Inspection Services-Veterinary Services. We thank SCWDS member state wildlife management agencies, the US Geological Survey Ecosystems Mission Area, and the US Fish and Wildlife Service for their long-term financial support.

## SUPPLEMENTARY MATERIAL

Supplementary material for this article is online at http://dx.doi.org/JWD-D-24-00077.

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