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SPATIAL EPIDEMIOLOGY OF CHRONIC WASTING DISEASE IN WISCONSIN WHITE-TAILED DEER

Damien O. Joly,[1,7,8] Michael D. Samuel,[2] Julia A. Langenberg,[3] Julie A. Blanchong,[1] Carl A. Batha,[4] Robert E. Rolley,[5] Delwyn P. Keane,[6] and Christine A. Ribic[2]

[1] Department of Wildlife Ecology, University of Wisconsin–Madison, 1630 Linden Dr., Madison, Wisconsin 53706, USA
[2] USGS Wisconsin Cooperative Wildlife Research Unit, Department of Wildlife Ecology, University of Wisconsin–Madison, 1630 Linden Dr., Madison, Wisconsin 53706, USA
[3] Wisconsin Department of Natural Resources, 101 S. Webster St., Madison, Wisconsin 53703, USA
[4] Wisconsin Department of Natural Resources, 1500 N. Johns St., Dodgeville, Wisconsin 53533, USA
[5] Wisconsin Department of Natural Resources, 1350 Femrite, Monona, Wisconsin 53716, USA
[6] Wisconsin Veterinary Diagnostic Laboratory, 6101 Mineral Point Rd., Madison, Wisconsin 53705, USA
[7] Current address: Fish and Wildlife Division, Alberta Sustainable Resource Development, 6909 116 Street, Edmonton, Alberta T6H 4P2, Canada
[8] Corresponding author (email: damien.joly@gov.ab.ca)

ABSTRACT: Chronic wasting disease (CWD) is a fatal, emerging disease of cervids associated with transmissible protease-resistant prion proteins. The potential for CWD to cause dramatic declines in deer and elk populations and perceived human health risks associated with consuming CWD-contaminated venison have led wildlife agencies to embark on extensive CWD control programs, typically involving culling to reduce deer populations. We characterized the spatial distribution of CWD in white-tailed deer (*Odocoileus virginianus*) in Wisconsin to facilitate CWD management. We found that CWD prevalence declined with distance from a central location, was locally correlated at a scale of 3.6 km, and was correlated with deer habitat abundance. The latter result is consistent with patterns expected for a positive relationship between density and prevalence of CWD. We recommend management activities focused on culling in geographic areas with high prevalence to have the greatest probability of removing infected individuals. Further research is needed to elucidate the factors involved in CWD spread and infection rates, especially the role of density-dependent transmission.

Key words: Chronic wasting disease, disease management, spatial analysis, white-tailed deer.

INTRODUCTION

Chronic wasting disease (CWD) is an emerging prion disease of mule deer (*Odocoileus hemionus*), white-tailed deer (*Odocoileus virginianus*), and elk (*Cervus elaphus*) in North America (Williams and Miller, 2001; Williams et al., 2002). Affected deer and elk are not known to recover from this neurodegenerative disease. The potentially detrimental long-term effects of CWD on growth of affected free-ranging cervid populations (Gross and Miller, 2001), human health concerns associated with consumption of venison from CWD-affected deer and elk (Davanipour et al., 1986; Belay et al., 2004), and related concerns about the economic consequences of the presence of CWD in deer and elk populations have led management agencies to seek effective strategies to control CWD distribution and prevalence.

In the absence of a treatment or vaccine for CWD in deer and elk, the main tool available for CWD control in free-ranging populations is selective culling of affected individuals or nonselective culling of deer in affected areas (Williams et al., 2002). The goals of these culling programs have been to reduce the population impact by reducing prevalence of CWD or to eliminate the disease from smaller geographic areas where CWD has been recently introduced. The assumption underlying both of these strategies is that population reduction will reduce contacts between affected and susceptible individuals and consequently reduce the disease transmission rate. Furthermore, if populations can be reduced below a theoretical threshold (the critical community size),

transmission would be insufficient to maintain the disease (Anderson and May, 1991). Alternatively, if transmission rates are not density-dependent, a reduction in density theoretically will not reduce prevalence, and there is no theoretical minimum host density for disease persistence (Getz and Pickering, 1983; reviewed by Lloyd-Smith et al., 2005). Consequently, determining the nature of the density-transmission relationship is important to predict the amount of culling required and the consequences of disease management programs (McCallum et al., 2001).

It is not known whether transmission of CWD is density-dependent. Initial modelling studies of CWD in free-ranging cervids assumed that transmission of CWD would be independent of density (Miller et al., 2000; Gross and Miller, 2001); this assumption is based on the social behavior of cervids. Because female white-tailed deer associate within matrilineal social groups while males tend to be alone or in small groups outside the breeding period (Nixon et al., 1991), these social groups may not change in size with deer density. However, changes in population density or size (Borowski, 2000; Hebblewhite and Pletscher, 2002) may affect the frequency and intensity of interactions among deer within or among social groups (Hirth, 1977; Nixon et al., 1991; Grenier et al., 1999; Kie and Bowyer, 1999).

Because CWD is either directly transmitted from animal to animal or indirectly through an environmental route (Miller and Williams, 2003; Miller et al., 2004), knowledge of the spatial patterns of CWD may be useful to direct culling operations. Preliminary sampling suggests that there is a clustered spatial distribution of diseased animals in the CWD-affected area of south-central Wisconsin (Joly et al., 2003), and this indicates that deer in proximity to positive deer are more likely to be positive. Therefore, concentrating culling efforts in areas with high prevalence will not only result in a direct reduction in overall prevalence (by disproportionately killing CWD-positive deer relative to the larger population), but may also reduce density-dependent transmission and the potential for environmental contamination.

The objectives of our research were to describe the spatial distribution of CWD in white-tailed deer in southern Wisconsin and evaluate factors associated with CWD prevalence to facilitate disease management actions.

MATERIALS AND METHODS

Tissue collection and CWD testing

From 1 September 2002 to 1 March 2004, white-tailed deer heads were collected from hunter-killed deer at registration stations (October–November) and from deer collected by government sharpshooters (throughout the year); all deer were sampled within the 1,805 km^2 "disease eradication zone" (DEZ) in south-central Wisconsin (Fig. 1). To test for a year effect, the study period was divided into two periods, the first including data collected between 1 September 2002 and 31 March 2003, the second being 1 April 2003 to 1 March 2004. The DEZ was defined as extending 7.25 km in radius from CWD-positive deer identified by 1 September 2002, with minor extensions to roads and other recognizable boundaries. Location of harvest (to the Public Land Survey System "section," 2.6 km^2), age, sex, and date of harvest were recorded. Retropharyngeal lymph nodes and obex were removed and stored in 10% formalin or frozen for diagnostic testing at the Wisconsin Veterinary Diagnostic Laboratory (WVDL). In 2002/2003, immunohistochemical (IHC) staining was used to detect the presence of protease-resistant protein, PrP^{cwd} (Miller and Williams, 2002). In 2003/2004, some deer were tested using IHC, but most were tested using an ELISA-based screening test (IDEXX Laboratories Inc., Westbrook, Maine, USA) on frozen lymph nodes, with any initial positives confirmed by IHC. In both years retropharyngeal lymph nodes were initially tested; if positive, IHC was conducted on lymph node and obex if available. Deer for which PrP^{cwd} was detected in retropharyngeal lymph nodes or obex were considered CWD-positive (Miller and Williams, 2002; Joly et al., 2003). Deer for which data (age, sex, location, CWD test result) were incomplete as well as deer < 1 yr old (due to

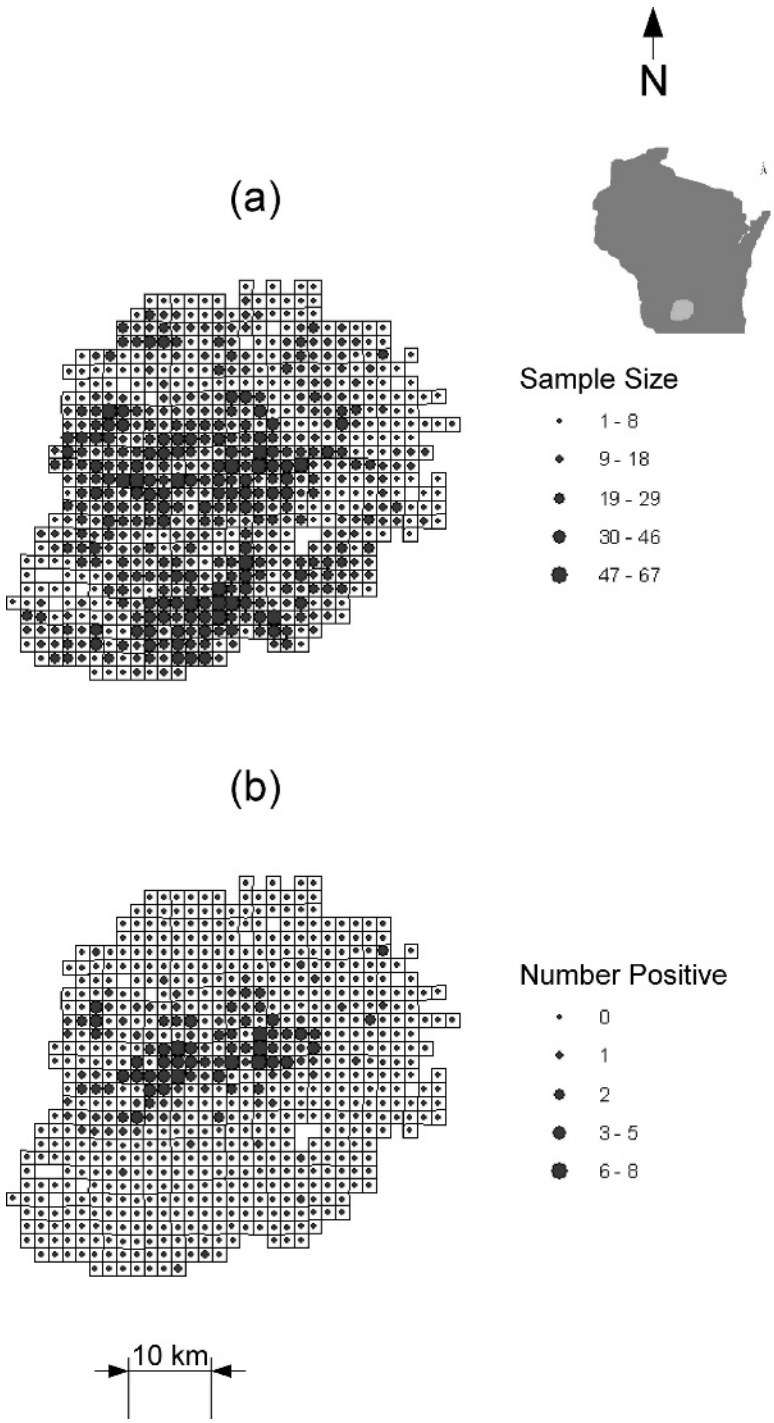

FIGURE 1. Spatial distribution of samples (a) and CWD-positive deer (b) in the disease eradication zone in south-central Wisconsin, 2002–04 (light shaded area in inset map of Wisconsin). Number of samples (n) and number of positive deer in each section (2.6 km^2).

TABLE 1. Descriptive statistics of test results for chronic wasting disease in white-tailed deer in the disease eradication zone in south-central Wisconsin. Data were collected in 2002/2003 and 2003/2004. Numbers and ranges in parentheses are standard deviations and 95% confidence limits, respectively. Only deer (>1 yr) for which we had data on sex, age, location of harvest, and a CWD-test result were included in the sample. Statistical tests refer to a test whether there was a change between study periods.

Statistic	Study period: 1 September 2002–31 March 2003	Study period: 1 April 2003–1 March 2004	Statistical test
Number of deer harvested (>1 yr)	6,664	4,331	
Number of deer harvested (<1 yr)	4,159	981	
Number of CWD-positive deer (<1 yr)	6	0	
Prevalence in deer <1 yr	0.001 (0.0005–0.003)	0 (0–0.004)	χ^2=0.45, P=0.50
Sample size	6,436	4,242	
Number of CWD-positive deer in sample	152	94	
Prevalence in sample	0.023 (0.02–0.027)	0.022 (0.018–0.027)	χ^2=0.17, P=0.68
Overall average age in sample (yr)	2.19 (1.5)	1.97 (1.26)	t=8.46, P<0.001
Average age in sections (yr)	2.04	1.96	Average difference=0.045, $CI_{95\%}$=0.125–0.035
Overall sex ratio (% males) in sample	45%	51%	χ^2=1.35, P<0.001
Average sex ratio (% males) in sections	44%	52%	Average difference=0.06, $CI_{95\%}$=0.035–0.09

very low prevalence in that age class) were excluded from analysis (Table 1).

Evaluation of the different sampling periods

Data collected in each sampling period were examined for a systematic difference in prevalence or in those factors that could affect prevalence. Potential age differences between years were tested using a t-test; a potential difference in the sex ratio between years was tested using a χ^2 test (Sokal and Rohlf, 1995). We also checked for differences in average age and sex ratio (% males) in sections by calculating the average age and sex ratio for each section, and calculating the average difference between 2002/2003 and 2003/2004. We considered there to be a change in the sample between the years if the 95% confidence interval for this difference did not overlap zero. We tested for a difference in prevalence with year by comparing overall prevalence using a χ^2 test, and then calculated the difference in prevalence for each section between years and considered there to be an overall change if the 95% confidence limits for the average difference did not include zero. If there are seasonal changes in prevalence (Conner et al., 2000), bias could result if the temporal distribution of samples changed between the years. We also tested for a change in temporal distribution in prevalence from 2002/2003 to 2003/2004 by calculating estimated prevalence on each day of the period for each year and compared distributions using a Kolmogorov-Smirnov test (Sokal and Rohlf, 1995). For analysis, we pooled prevalences for the 2 yr if there was no systematic difference in prevalence between the two study periods.

Spatial pattern

We determined if prevalence was uniform within the sample by using the spatial scan statistic (Kulldorff and Nagarwalla, 1995; Joly et al., 2003). The spatial scan statistic used a Poisson likelihood model to identify regions of higher and lower expected number of CWD-positive deer, relative to the total sample, by comparing the observed number of CWD-positive deer in 10,000 randomly placed circles to what would be expected if there was no spatial variation in prevalence. Early in an epidemic of an emerging infectious disease, we would expect prevalence to be

highest in areas where the disease has been present the longest. If we assume that CWD was introduced at a central location and spread from there, the distance from that location could serve as a surrogate for time since introduction. We used the results of the scan statistic to define a "core affected area" for the disease eradication zone and assumed that disease was introduced at the center of this area.

Correlates of CWD prevalence

We assessed the correlation between CWD prevalence (defined as the proportion of deer in a section that test positive for CWD, synonymous with apparent prevalence) and several ecological factors that we hypothesized would be related to infection rates. Directly estimating transmission rates in relation to density is extremely difficult, so we used a common approach to evaluate indirectly the role of density in disease transmission by relating density to disease prevalence (McCallum et al., 2001). Specifically, we examined the relationship between prevalence of CWD and deer habitat abundance (as a surrogate for density). We used deer habitat as a surrogate for density because it was not possible to obtain deer density at the section level, and deer habitat was previously shown to be a good predictor of deer density in this study area (Blanchong et al., in press). The variable was entered into the analysis as the proportion of each section in deer habitat. Deer habitat was defined as 1) forest, shrubland, and wetland >4 hectares, 2) forest, shrubland, and wetland >1 hectare in size within 200 m of larger tracts of the same, and 3) agriculture and grassland within 100 m of forest, shrubland, and wetland.

We estimated the effect of various factors on apparent CWD prevalence in each section by fitting a Gaussian geostatistical model (Ribeiro and Diggle, 2001; Diggle et al., 2003) of the general form

$$\ln((Pi + 0.01)/(1 - Pi + 0.01)) = \beta \cdot Xi + Si + e, \quad (1)$$

where P_i is the proportion of deer in section i that were CWD-positive, (logit-transformed to meet the assumptions of the Gaussian model, plus a constant, 0.01, to accommodate sections where $P_i=0$), X_i is a matrix of covariates with associated coefficients (β), S_i is a stationary spatial Gaussian process (exponential model) with variance σ^2 (partial sill) and ϕ (range), and e is the error term with variance parameter τ^2 (nugget variance) (Diggle et al., 2003). The terms S_i and e were included in all models to account for local spatial autocorrelation. We fitted four, nested models of CWD prevalence in each section: 1) a null model with no covariates, 2) proportion each section that is classified as deer habitat as a surrogate for deer density, 3) distance (km) from the center of the core affected area as a surrogate for time since CWD introduction, and 4) deer habitat and distance. As there is no a priori reason for CWD to spread equally in all directions, we tested for directional spread by coding each section with a categorical variable indicating whether the section was northeast, northwest, southeast, or southwest of the center of the core affected area, and tested whether the change in prevalence with distance differed among these quadrants.

We also modeled the interaction between distance and the directional quadrant variable (northeast, northwest, southeast, southwest) to test for directional spread of CWD. As prevalence estimates may be affected by the age and sex composition of the sample (Heisey et al., in press), we fitted all models a second time including average age and sex ratio (% males) to control for their potential confounding effect. Model selection was conducted by ranking the models by their Aikaike Information Criteria (AIC) values and using the minimum AIC model as the best model (Burnham and Anderson, 2002).

RESULTS

Comparison of the different sampling periods

Between 1 September 2002 and 1 March 2004, CWD status, age, sex, and location of kill were determined for 10,678 deer (>1 yr of age) removed from 648 of 697 sections (1,805 km^2) of the DEZ (Fig. 1); these included 6,436 and 4,242 deer in 2002 and 2003, respectively (Table 1). Most deer were collected between October and December of each year. Although there was a slight decline in mean age and an increase in sex ratio (% males) from 2002 to 2003, there was no consistent change in overall prevalence (Table 1) or prevalence by section (average difference between the years 0, $CI_{95\%}$ −0.01–0.01). There also was no difference in the temporal distribution of prevalence (Kolmogorov-Smirnov test, $D=0.0767$, $P=0.73$). Therefore, data from 2002 and

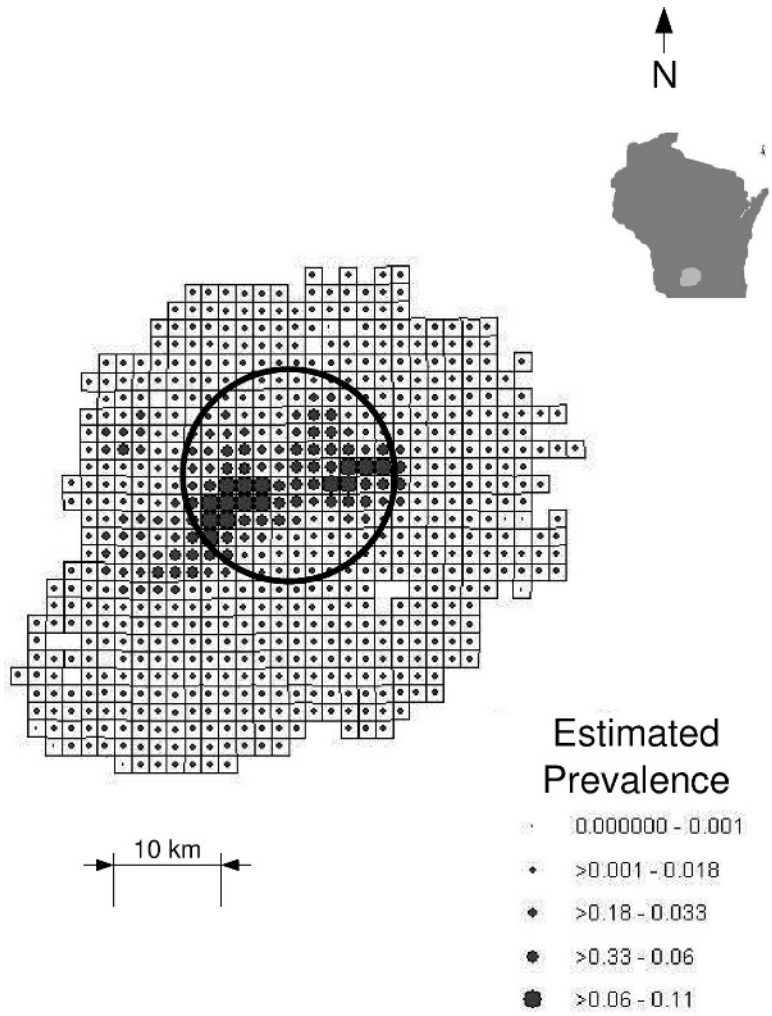

FIGURE 2. Spatial pattern of CWD prevalence in the disease eradication zone in south-central Wisconsin, 2002–04 (light shaded area in inset map of Wisconsin). The circle indicates the core affected area found using the spatial scan statistic. The center of the circle was assumed to be the hypothetical introduction site. Prevalence was estimated using model-based ordinary kriging, using the best model in Table 2.

2003 were pooled for analysis. Of the 10,678 deer tested, 246 (overall prevalence 2.3%, $CI_{95\%}$ 2.0–2.6%) tested positive for CWD.

Spatial pattern and correlates of CWD prevalence

The spatial scan statistic identified the core affected area as 117 sections (303 km^2) in the center of the DEZ (Fig. 2). Prevalence in the core affected area was estimated to be 6.2% (n=2567, $CI_{95\%}$ 5.3–7.2%). This was six times higher than in the remaining sections of the DEZ, where prevalence was estimated to be 1.1% (n=8,111, $CI_{95\%}$ 0.9–1.3%). The best model of prevalence in sections included terms for distance from the center of the core affected area and proportion of section in deer habitat (Table 2). Prevalence declined with distance from the center of the core affected area (odds ratio 0.963, $CI_{95\%}$ 0.962–0.964) and increased with increased area of deer habitat (odds ratio 1.0035, $CI_{95\%}$ 1.0034–

TABLE 2. Models tested as predictors of CWD prevalence in white-tailed deer in sections in the disease eradication zone in south-central Wisconsin. Data were collected in 2002/2003 and 2003/2004. Relative Akaike information criteria (ΔAIC) are provided, relative to the best fitting model (Burnham and Anderson, 2002). Spatial autocorrelation was accommodated in all models (see Equation 1). Habitat refers to the proportion of deer habitat in each section as a surrogate for deer density, distance refers to the distance from the center of the core affected area defined by a spatial scan statistic, and distance by quadrant is a model where separate coefficients are estimated for decline in prevalence with distance in northwestern, northeastern, southwestern, and southeastern quadrants.

Terms	ΔAIC	
	Average age and sex ratio (% males) not included in model	Average age and sex ratio (% males) included in model
Deer habitat, distance	0	3.46
Deer habitat	5.09	8.47
Deer habitat, distance by quadrant	5.23	8.67
Distance	5.71	9.25
Distance by quadrant	10.87	14.42
Intercept only	12.92	16.41

1.0036; Fig. 3). The decline in prevalence with distance from the core area did not appear to vary by direction (models including that term increased AIC by 5.23 to 10.87 units). Inclusion of average age and sex ratio did not improve model fits (AIC increased 3.37–3.55 units). The range of spatial autocorrelation in the best-fit model was 3.58 km. Using the best-fit model (Table 2), we created a model-based, kriged surface of CWD prevalence (Fig. 2). This prevalence surface suggested two areas of increased prevalence within the core affected area, accounting for the apparent nonmonotonic decline in prevalence with distance from the center (Fig. 3).

DISCUSSION

We found that the spatial pattern of CWD in white-tailed deer in south-central Wisconsin had both broad-scale and local components. Overall, prevalence declined with distance from the center of the affected area, a pattern that is consistent with an earlier analysis on a subset of these data (Joly et al., 2003) and consistent with other horizontally transmitted diseases, such as bovine tuberculosis in Michigan white-tailed deer (Hickling, 2002). We also found that prevalence was positively correlated with amount of deer habitat. In contrast, we did not find evidence for directional spread of CWD that was not accounted for by deer habitat; the appearance of increased prevalence to the southwest (Fig. 2) may be related to increased deer habitat as suggested by our analysis, not innate directional spread. Locally, prevalence in each section was spatially correlated with prevalence in sections up to 3.6 km away. Local spatial autocorrelation is often attributed to unmeasured variables or sampling error; if all possible variables were measured with perfect accuracy, there would be no spatial autocorrelation (Cressie, 1993). We suspect that some spatial autocorrelation also can be attributed to our choice of the section as the unit of analysis. This is an artificial boundary for mobile deer that likely move and interact with deer outside the section in which they were collected.

Our results suggest prevalence of CWD at any particular point is correlated with distance from the introduction point (as a surrogate for time required for disease spread or "disease history") and local environmental characteristics (e.g., deer habitat). We recognize that density and history are not mutually exclusive. With density-dependent transmission a disease is more likely to first become established

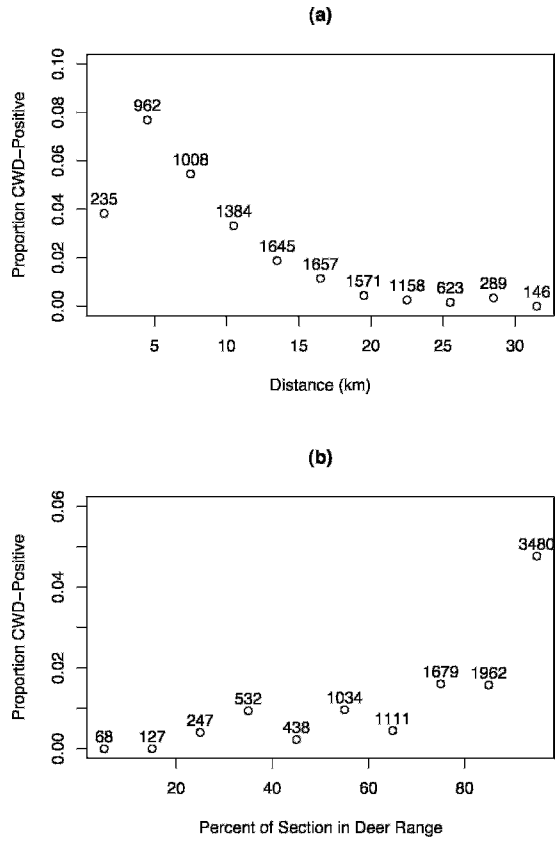

FIGURE 3. Relationship between proportion of CWD-positive deer and a) distance from center of the core affected area and b) proportion of each section in deer habitat. To facilitate interpretation, sections were binned (by increments of 3 km and 0.10 for distance and deer habitat, respectively) and displayed by midpoint of bin. Numbers of points indicate the number of sections in each bin.

in a locally dense population. However, in our analysis, the model including surrogates for both factors fit the data substantially better than models with either alone. Consequently, we hypothesize that both history and density are acting to affect prevalence of CWD.

We hypothesized that CWD transmission rates may be related to deer density based on the habitat–prevalence relationship. Because we have used surrogates for both deer density (deer habitat) and disease transmission rates (CWD prevalence), we have not strictly tested for density dependence in the transmission rate. Factors not strictly related to density such as breeding behavior, social interactions, and movement patterns of deer (we do not have measures for these) affect contact rates and thus also may play an important role in determining rates of CWD transmission. Because each of these factors may be affected by deer density, the actual mechanism generating a density-prevalence relationship is yet unknown. We also suspect that the relationships among deer density, social structure, and contact rates are also influenced by practices that artificially concentrate deer such as supplemental feeding and baiting (Garner, 2001), which may increase disease transmission (Hickling, 2002; Miller et al., 2003; Farnsworth et al., 2005). Furthermore, a nonlinear relationship between density and contact rate may prevent a linear reduction in disease

transmission as a population declines. Evidence of density-dependent transmission implies a minimum host density for disease persistence; however, we note that evidence for such density thresholds in other disease systems is limited (Lloyd-Smith et al., 2005). Further research that directly measures or experimentally manipulates deer density is necessary to elucidate the role of density in CWD prevalence and transmission.

Although direct evidence for a density-dependent transmission relationship is weak, comparison of prevalence rates from wild and captive outbreaks suggest that CWD transmission may be facilitated at higher cervid densities. Consequently, there may be a higher risk of CWD becoming established if introduced to high-density populations and if it persists, increasing to relatively high densities. Therefore, we recommend that managers consider high-density cervid populations as "high risk" when planning CWD surveillance and management programs (Samuel et al., 2003). Furthermore, we recommend that those jursidictions attempting to control CWD through density reduction closely monitor some index of disease transmission such as prevalence, or perhaps more appropriately, force of infection (Heisey et al., in press) to test the hypothesis of density-dependent transmission for CWD.

Even in the absence of density dependence, population reduction may be a viable CWD management option because of the spatial structure of CWD in a population. Population simulation indicates that test-and-cull operations can reduce CWD prevalence (Gross and Miller, 2001); however, these activities require antemortem knowledge of CWD status in individual deer and thus are not practical in large areas. Our analysis indicated that CWD is clustered on the landscape, from which one could infer that deer near CWD-positive deer are more likely to be positive. Consequently, we propose that knowledge of the spatial distribution of CWD could substitute for knowledge about the disease state of individual deer. Specifically, the effect of culling deer in high-prevalence areas could be to reduce survival of deer that are more likely to be CWD-positive than those in low-prevalence areas, mimicking the effect of a test-and-cull operation. The effectiveness of the use of such targetted culling could easily be examined through population simulation.

Several questions remain about how CWD spreads in white-tailed deer populations that have important implications for management of this disease. CWD may spread in white-tailed deer populations along corridors of deer habitat, and higher prevalence may be achieved in areas with higher deer density. Although we do not know the main factor(s) driving expansion at the periphery of the affected area, we suspect that expansion may be driven by factors related to juvenile dispersal, movement of adult deer, and disease spread among matriarchal social groups. There were several CWD-positive deer found on the periphery of the affected area described herein (WDNR, unpubl. data). At present, we do not know if these apparently isolated "sparks" of prevalence are representative of the tails of a continuous decline in prevalence or are new foci discontinuous with the main outbreak. If these outlying cases represent new foci of infection, additional culling effort may be required in their vicinity to prevent further expansion.

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