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EPIDEMIOLOGY OF CHRONIC WASTING DISEASE IN FREE-RANGING MULE DEER: SPATIAL, TEMPORAL, AND DEMOGRAPHIC INFLUENCES ON OBSERVED PREVALENCE PATTERNS

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ABSTRACT: We analyzed chronic wasting disease (CWD) prevalence data from mule deer populations in northcentral Colorado, USA, to discern the likely influences of temporal, spatial, and demographic factors on patterns observed in naturally infected populations. In addition to reaffirming spatial heterogeneity among wintering mule deer subpopulations, we report marked differences in CWD prevalence by sex and age groups as well as clear local trends of increasing prevalence over a 7-yr period. Prevalence of CWD differed by age (yearling vs. adult), sex, and geographic area at two different spatial scales (game management unit or population unit winter range) and increased over time at both geographic scales. Disease status (positive or negative) was not independent of age for males ($n = 285$, df = 6, $\chi^2 = 18.4$, $P = 0.005$) or females ($n = 387$, df = 8, $\chi^2 = 17.2$, $P = 0.028$). Among males, prevalence increased and then declined across age classes, peaking in 5- to 6-yr-old individuals; among females, prevalence showed no definite age-related pattern. Demographic, spatial, and temporal factors all appear to contribute to the marked heterogeneity in CWD prevalence in endemic portions of northcentral Colorado, USA. These factors likely combine in various ways to influence epidemic dynamics on both local and broad geographic scales.

Key words: Chronic wasting disease (CWD), mule deer, *Odocoileus hemionus,* prion, transmissible spongiform encephalopathy.

INTRODUCTION

Chronic wasting disease (CWD) (Williams and Young, 1980), a contagious prion disease of deer (*Odocoileus* spp.) and wapiti (*Cervus elaphus nelsoni*), has emerged as an important wildlife health problem in several parts of North America (Williams and Miller, 2002; Williams et al., 2002). Epidemics of CWD appear to be self-sustaining, with transmission likely occurring in both the presence and absence of live, infected animals and infectious agents persisting in contaminated environments (Williams and Young, 1992; Miller et al., 1998, 2000, 2004; Williams and Miller, 2002; Miller and Williams, 2003; Miller and Wild, 2004). Based on studies of natural and experimental transmission in captive cervids, susceptibility to CWD appears to be relatively uniform both between sexes and across age classes within the three host species (Williams and Young, 1980, 1982, 1992; Miller et al., 1998, 2004; Williams and Miller, 2002; Miller and Wild, 2004).

Because CWD in free-ranging cervids was only recognized approximately 25 yr ago (Spraker et al., 1997), few data are available for studying temporal, spatial, and demographic influences on epidemic dynamics in natural populations. The most extensively studied "endemic" focus of CWD in free-ranging cervid populations occurs in northeastern Colorado and southeastern Wyoming, USA. In this area, mule deer (*Odocoileus hemionus*) are the predominant host species (Miller et al., 2000). Initial analyses of epidemiologic data from this "endemic area" suggested both spatial and demographic influences on observed patterns of CWD prevalence in mule deer: Prevalence varied at a coarse geographic scale and appeared to be higher in middle-aged mule deer than in either younger or older age classes (Miller et al., 2000). Subsequent study of mule deer movement patterns in northcentral Colo-

rado revealed marked heterogeneity in CWD prevalence across relatively insular wintering subpopulations of mule deer and suggested that interaction of these distinct "population units" may largely explain observed spatial heterogeneity (Conner and Miller, 2004). Better understanding of temporal and demographic influences on epidemic dynamics would complement improved resolution of the spatial epidemiology of CWD. Moreover, insights regarding temporal trends and demography could be useful in refining strategies for controlling epidemics in free-ranging wildlife.

Here, we describe analyses of CWD prevalence data from mule deer populations in northcentral Colorado to discern the likely influences of temporal, spatial, and demographic factors on patterns observed in naturally infected populations. In addition to reaffirming spatial heterogeneity among wintering mule deer subpopulations, we report marked differences in CWD prevalence by sex and age groups as well as clear local trends of increasing prevalence over a 7-yr period.

MATERIALS AND METHODS

Study area

We studied CWD epidemiology in a 7,100-km^2 area in northcentral Colorado (Fig. 1) where CWD is endemic in free-ranging cervids (Miller et al., 2000). Elevation ranged from 1,400 m in eastern portions to 4,300 m in western portions of this area. The northeastern quarter of our study area, from Fort Collins northward, consisted of rolling foothills and high prairie where livestock grazing was the main land use. Vegetation was primarily sagebrush-steppe habitat, with big sagebrush (*Artemisia tridentata*), antelope bitterbrush (*Purshia tridentata*), mountain mahogany (*Cercocarpus montanus*), and mixed grasses. The southeastern quarter of this area, from Fort Collins southward, consisted of urban centers separated by rural areas, with numerous small ranches and agricultural fields, as well as some suburban areas. In the western half of our study area, vegetation changed across an elevation gradient. Vegetation types ranged from mainly dense stands of mountain mahogany interspersed with grassland openings and small timbered patches of ponderosa pine (*Pinus ponderosa*) to mountain shrub habitat with a ponderosa pine and Douglas fir (*Pseudotsuga meziesii*) overstory that gave way at the highest elevations to alpine tundra.

Our study area was inhabited by mule deer, white-tailed deer (*Odocoileus virginianus*), and wapiti. This study area has been administratively divided into game management units (GMUs) by the Colorado Division of Wildlife (CDOW) to aid in deer and wapiti population management by distributing harvest pressure. The GMU boundaries typically run along roads or county boundaries (for simplicity and convenience rather than for biological relevance). We used GMUs as historical and commonly used spatial units to assess spatial aspects of CWD epidemiology, and we collected data from 6 GMUs within this study area (Fig. 1). However, distinct subpopulations (subsequently termed "population units") occur within each GMU (Conner and Miller, 2004). Because we wanted to assess spatial differences at a more biologically relevant scale, we also analyzed data from specific winter ranges for 12 mule deer population units within the study area (Fig. 1), as described below.

Data collection

To fully evaluate demographic influences on prevalence, our approach to analysis was comprised of three elements, each using a separate data subset. First, to fully evaluate age, sex, temporal, and coarse-scale spatial effects, we used all data from yearling and adult mule deer in the study area. Second, to compare epidemiologic differences in biologically defined population units, represented by mule deer winter ranges, we used a subset of data from samples collected within winter ranges of 12 previously defined mule deer population units (Conner and Miller, 2004). For these first two analyses, we classified sampled deer as either "yearling" (age, ~1.3–1.9 yr) or "adult" (age, ≥2 yr) based on visual inspection. Finally, we performed a more rigorous analysis of sex- and age-related differences in CWD prevalence based on a subset of data from deer in which age (in yr) was estimated via counts of tooth cementum annuli. We describe analyses for each separately, but we begin with a description of methods common to all three data sets.

We used georeferenced data from ongoing CWD surveillance, management, and research programs to estimate local CWD prevalence throughout the study area. Sampled mule deer were classified as CWD-positive (infected) or CWD-negative (uninfected) based on immunohistochemical examination of retropharyngeal lymph node or tonsil tissue (Miller and

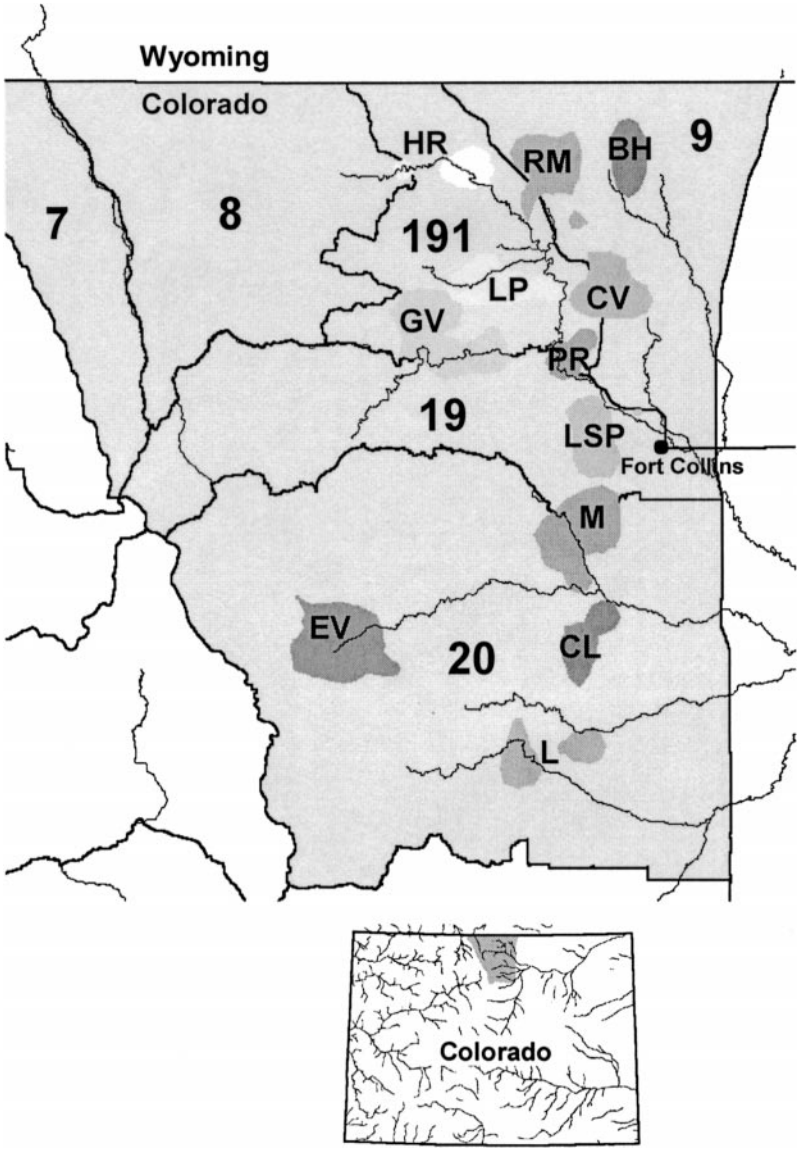

FIGURE 1. Study area in northcentral Colorado, USA, with six game management unit (GMU) boundaries and winter ranges of 12 mule deer subpopulations (population units) (Conner and Miller, 2004). Numbers (7, 8, 9, 19, 20, and 191) designate GMUs; letters refer to population units, named by a local geographic feature: Big Hole (BH), Carter Lake (CL), Campbell Valley (CV), Estes Valley (EV), Glacier View (GV), Halligan Reservoir (HR), Lyons (L), Lone Pine (LP), Lory State Park (LSP), Masonville (M), Poudre River (PR), and Red Mountain (RM).

Williams, 2002); CWD surveillance and diagnostic methods were performed as described elsewhere (Miller et al., 2000; Miller and Williams, 2002; Wolfe et al., 2002; Hibler et al., 2003). Sources of tissue samples included mule deer killed by hunters during September 1996–January 2003 (Miller et al., 2000; Miller, unpubl.), apparently healthy mule deer killed by wildlife managers during December 2001–January 2003 (Miller, unpubl.), and mule deer that were captured and underwent tonsil biopsy during March 2001–January 2003 (Wolfe et al., 2002, 2004; Wolfe and Miller, unpubl.). Because data from symptomatic animals are highly biased (Miller et al., 2000), data from "targeted" surveillance (Miller et al., 2000) were excluded from these analyses. Only data from mule deer ≥1.3 yr old were used to estimate

prevalence (Miller et al., 2000; Williams and Miller, 2002; Miller and Williams, 2003), except in explicit comparisons among age classes. All annual estimates of CWD prevalence were based on a biological year, defined as 15 June–14 June. The sample size (n) was the number of mule deer sampled.

We used model selection to test hypotheses about differences in probability of CWD infection by sex, age, space, and time. Because the CWD test result (positive or negative) was coded as a binary response variable, we used logistic regression models for these analyses (Agresti, 1996). For all model selection, we followed the methods described by Burnham and Anderson (2002) to select an appropriate model. We used Akaike's Information Criterion (Akaike, 1973) corrected for small sample bias (AICc) as the basis for objectively ranking models and selecting an appropriate "best approximating" model (Burnham and Anderson, 2002). We ranked and compared models using ΔAICc (Leberton et al., 1992; Burnham and Anderson, 2002) and normalized AICc weights ($\hat{w}_m$) (Buckland et al., 1997; Burnham and Anderson, 2002). Models that were ≤2 AICc units removed from the best model were considered to be competing models. Models that were 2–4 AICc units removed were considered to be reasonably plausible models, and models that were more than 4 AICc units removed were considered to be poor representations of our data (Burnham and Anderson, 2002). We calculated AICc values and model-averaged parameter estimates using computerized statistical software (SAS Institute, 1993).

In the face of model uncertainty, we used model averaging to account for model variation and to estimate prevalence more robustly (White et al., 2001; Burnham and Anderson, 2002). We calculated model-averaged estimates of CWD prevalence for each year by sex, age, and relevant spatial units across all models considered. Because all models were logit models, model-averaged CWD prevalence estimates were calculated in the logit scale and back-transformed to calculate appropriate confidence intervals (CIs), which were slightly asymmetric (Burnham and Anderson, 2002).

Patterns at a coarse geographic scale

From previous data analyses (Miller et al., 2000), we knew that CWD prevalence varied by GMU and age (yearling vs. adult). Previous analyses also suggested that prevalence varied little between male and female mule deer, but because so few females were sampled during 1996–99 and most came from a relatively small proportion of the overall study area, we suspected that this result may have stemmed from a lack of power and sampling distribution rather than from a true lack of difference. Consequently, we wanted to reevaluate whether CWD prevalence was different between male and female mule deer. To evaluate prevalence differences between the sexes, a larger sample of females was collected during 2000–02 in conjunction with increased harvest and culling pressure. In addition, we wanted to evaluate whether CWD prevalence had increased in our study area.

To answer these questions, we began data analyses with a set of models that included sex, age (1 yr or ≥2 yr), GMU, and temporal effects. We could not use finer-scale age data in the present study, because such data were estimated from a subset of animals for which age was determined via tooth cementum annuli collected in a case-control design (Agresti, 1996) and, thus, were not available for each individual. We initially represented temporal effects as either a monotonic trend over time ("trend") or as year-to-year variation in prevalence without a clear trend, modeled as a categorical variable ("time"). A large number of potential models were conceivable if every combination of age, sex, GMU, and year effects plus their interactions were considered. We did not want to run a large number of models because of the unknown significance problems associated with this sort of approach (Burnham and Anderson, 2002), but we did not know how the probability of infection varied by sex, age, GMU, and time and did not want to exclude inadvertently a model that might best approximate the underlying processes. To balance the pitfalls of over- and underfitting our data, we decided to run 16 a priori models (Table 1) that we hypothesized might best approximate the structure of these data based on previous analyses and our understanding of mule deer biology. Based on previous observations (Miller et al., 2000; Wolfe et al., 2004), we further hypothesized that prevalence would increase faster in males, adults, and GMUs with higher prevalence. Consequently, we included interaction terms to test these hypotheses (models 5, 7, and 12); in all interaction models, we only used the monotonic trend to represent temporal effects. We also tried two models with third-order interactions (GMU×age×year and GMU×sex×year [models 8 and 13, respectively]) to fully test whether groups with high prevalence had a greater rate of increase in CWD prevalence over time compared to groups with lower prevalence. After analyzing these 16 a priori models (and to address reviewer comments), we constructed five additional models (models 17–21) (Table 1) to see whether better

TABLE 1. A priori (models 1–16) and post hoc (models 17–21) models relating sex, age, location, and temporal influences on prevalence of chronic wasting disease (CWD) in yearling and adult mule deer in north-central Colorado, USA, September 1996–April 2003.

Model	Hypothesis description	Model structure[a]
1	CWD prevalence varied by location	Location
2	CWD prevalence varied by location and sex in an additive manner	Location+sex
3	CWD prevalence varied by location and sex in a multiplicative manner	Location×sex
4	CWD prevalence varied by location and increased or decreased at the same rate for each location	Location+trend
5	CWD prevalence varied by location and increased or decreased at a different rate for each location	Location×trend
6	CWD prevalence varied by location and sex and increased or decreased at the same rate by sex and for each location	Location+sex+trend
7	CWD prevalence varied by location and sex additively and increased or decreased at different rates by sex and for each location	(Location+sex)×trend
8	CWD prevalence varied by location and sex multiplicatively and increased or decreased at different rates by sex and for each location	Location×sex×trend
9	CWD prevalence varied by location and varied without a trend from year to year	Location+time
10	CWD prevalence varied by location and sex additively and varied without a trend from year to year	Location+sex+time
11	CWD prevalence varied by location and age additively and increased or decreased at the same rate for each age group and for each location	Location+age+trend
12	CWD prevalence varied by location and age additively and increased or decreased at different rates by age and for each location	(Location+age)×trend
13	CWD prevalence varied by location and age multiplicatively and increased or decreased at different rates by age and for each location	Location×age×trend
14	CWD prevalence varied by location and age additively and varied without a trend from year to year	Location+age+time
15[b]	Using the structure of the top model from comparisons of models 1–14, add age or sex so that it has both effects	Location+sex+age+trend
16[b]	Using the structure of the top model from comparisons of models 1–14, add age or sex so that it has both effects	Location+sex+age+time
17[c]	Using the structure of the top model from comparisons of models 1–16, change the temporal structure to a quadratic trend	Location+sex+age+trend^2
18	Using the structure of the top model from comparisons of models 1–17, include a full age, sex, and temporal interaction that is additive with location	Location+(sex×age×trend^2)
19	Using the structure of the top model from comparisons of models 1–17, include an age and temporal interaction that is additive with location	Location+sex+(age×trend^2)
20	Using the structure of the top model from comparisons of models 1–17, include a sex and temporal trend interaction that is additive with location	Location+age+(sex×trend^2)
21	Using the structure of the top model from comparisons of models 1–20, change the temporal structure so that temporal influences varied from year to year without a trend	Location+age+(sex×time)

[a] "Location" influences were analyzed separately at two spatial scales: GMU = game management unit, or winter range. At each of these spatial scales, "sex" was male or female, and "age" was 1–1.9 y or >2 yr. Temporal influences were represented in three ways: as a linear trend over time ("trend"), as a quadratic trend over time ("trend^2"), or as year-to-year variation in prevalence without a clear trend, modeled as a categorical variable ("time").

[b] In comparing models 1–14, we found the two top models (models 11 and 14) had competing temporal structures but were within 0.8 ΔAICc units of each other and essentially equally supported by our data; consequently, we included both "trend" and "time" models in further comparisons.

[c] In comparing models 1–16, the top models at both spatial scales included "age+sex"; consequently, age and sex wee included in all subsequent models (Models 17–21) generated for further comparison.

explanatory hypotheses for patterns in the data could be supported. Specifically, model 17 tested the hypothesis that CWD prevalence increased nonlinearly as a quadratic trend over time ("trend^2"), and models 18–21 represented hypotheses that prevalence increased faster for males or adults in a more parsimonious manner than a priori models 7, 8, 12, and 13.

Patterns at a population unit scale

A subset of our data came from within winter ranges of 12 mule deer population units (Conner and Miller, 2004). These population units (Fig. 1) had been identified previously using cluster analysis based on radiotelemetry location data (Romesburg, 1984; SAS Institute, 1990; Bethke et al., 1996), and winter ranges had been estimated with 80% use contours based on winter locations of deer in the population units using a kernel home-range estimator and a least-squares, cross-validation procedure to estimate the smoothing parameter (Worton, 1989). Details of these analyses have been described by Conner and Miller (2004). To evaluate spatial and temporal patterns in CWD prevalence for winter range, we used the same models as those used for GMU analysis, but we replaced GMU classification with winter range classification for the spatial component (Table 1). Methods for model genesis, selection, and parameter estimation were as described above.

Demographic patterns from cementum annuli data

Each year, we submitted first incisors from CWD-positive harvested and culled deer and a subset of randomly selected CWD-negative deer for age (in yr) estimation via cementum annuli examination (Robinette et al., 1957; Erickson and Seigler, 1969; Larson and Taber, 1980). Although overall prevalence among deer used in this data set was biased high, because sample selection was a case-control design (Agresti, 1996), relative age-specific prevalence estimates were comparable within this data set. We tested whether being CWD positive was independent of age using a chi-square test. Initially, we considered three age classification schemes: 10 groups at annual increments (1 yr, 2 yr, . . ., 9 yr, or ≥10 yr), five broader age categories (1 yr, 2–3 yr, 4–6 yr, 7–9 yr, or ≥10 yr) (Miller et al., 2000), and two categories (1 yr or ≥2 yr, as applied in analyses described above). We performed model selection using AICc (Burnham and Anderson, 2002) (not shown) to determine which age classification scheme best represented the data, then used that grouping to estimate age-specific prevalence.

Because ages were estimated only for a subsample of adult deer, we used age distribution within the random subsample of cementum-aged deer to estimate the number and proportion of deer in each adult age and sex classification as

$$\hat{N}_i = N_n\hat{p}_{ni} + N_p\hat{p}_{pi},$$

where $\hat{N}_i$ was the estimated number of deer in each sex-age classification, N_n was the total number of negatives in the surveillance sample, $\hat{p}_{ni}$ was the proportion of negatives from the tooth-aged subsample in each sex-age classification, N_p was the total number of positives in the surveillance sample, $\hat{p}_{pi}$ was the proportion of positives from the tooth-aged subsample in each sex-age classification. Sex-age specific prevalence was estimated as

$$\hat{p}_i = \frac{N_p\hat{p}_{pi}}{\hat{N}_i} = \frac{\hat{N}_{pi}}{\hat{N}_i}$$

where $\hat{N}_{pi}$ was the estimated number of CWD-positive deer in each sex-age classification. To estimate variance, we applied the delta method (Seber, 1982), with the assumption that the number of positives was independent from the number of deer sampled for each sex-age classification.

To evaluate whether trends in prevalence were age-specific, we used logistic regression, with age and sex as the independent variables. Based on previous analyses (Miller et al., 2000; Grear et al., 2005), we constructed four biologically reasonable models: Two models in which sex was either additive with ln(age) or multiplicative with ln(age) represented "threshold" models in which prevalence rose and then plateaued (Grear et al., 2005), and two models in which sex was either additive with age and age^2 or multiplicative with age and age^2 represented "humped" models in which prevalence rose and then declined (Miller et al., 2000). We compared these four models to a "constant" model in which prevalence remained unchanged across age groups; this last model represented a null model. The constant model had a sex term that allowed prevalence to be constant but different for males and females. We used AICc model selection as described above to choose the best model (Burnham and Anderson, 2002) (not shown).

RESULTS

Patterns at a coarse geographic scale

We used data from 6,925 mule deer, including 470 (6.8%) that were CWD posi-

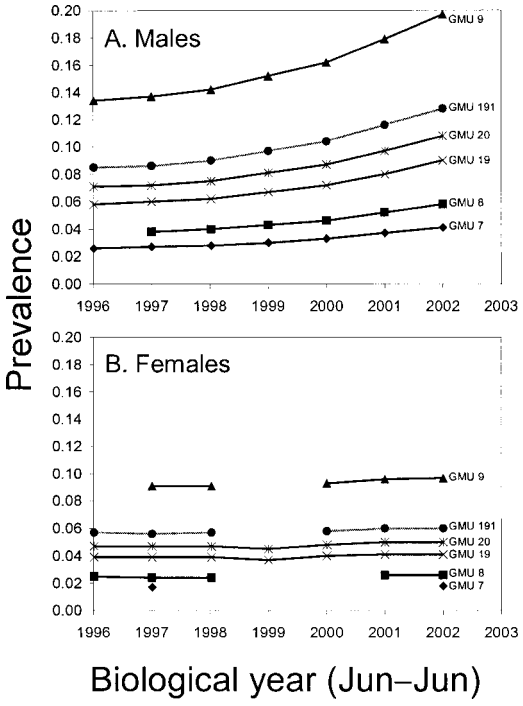

FIGURE 2. Model-averaged predicted values of chronic wasting disease (CWD) prevalence among mule deer for game management units (GMUs) in northcentral Colorado, USA, versus biological year for (A) adult males and (B) adult females (September 1996–April 2003). A biological year was defined as 15 June–14 June.

tive individuals, in analyses of sex, age, GMU, and time. Two of the models with temporal trend interaction (models 8 and 13) did not converge and were deleted from the model set, because model-fit statistics were not reliable (SAS Institute, 1993). Lack of convergence most likely occurred because of missing data for certain classifications (e.g., adult females in GMUs 7, 8, and 9 in 1999) (Fig. 2). The model (Table 2) that included effects of GMU, age, and an interaction of sex with a nonlinear temporal trend (model 20) enjoyed the strongest support; this model was 2.3–3.2 ΔAICc units from two somewhat less plausible models (models 17 and 15) (Table 2), accounted for 55% of the model weight, and was approximately two- to fourfold more likely than the latter two models based on AICc normalized model weight (Table 2). The top three models (models 20, 17, and 15) were the only plausible models and together accounted for 84% of the model weight; all included GMU ($P<0.0001$), sex, and age effects, plus an increasing trend in prevalence. In the top model, CWD prevalence was affected by age and GMU; temporal trends differed between sexes, increasing nonlinearly over time for males ($P = 0.0377$), but not for females ($P = 0.1382$), based on the trend and interaction terms. Model-averaged prevalence estimates also reflected these trends: Prevalence of CWD rose in a nonlinear fashion, and this rise tended to be more rapid among males than among females (Fig. 2).

Patterns at a population unit scale

We used data from 1,590 mule deer, including 159 (10%) that were CWD positive, in analyzing patterns both within and among winter ranges of 12 predefined population units. As in coarse-scale analyses, models 8 and 13 did not converge. Support among winter range-level models (Table 3) was similar to that seen in the GMU-level analyses (Table 2), suggesting that similar biologic processes influence CWD prevalence at both spatial scales. Four models (models 17, 15, 20, and 19) (Table 3) within 1.7 ΔAICc units of one another were comparably supported by winter range data and collectively accounted for 95% of the model weight. All four plausible models of winter range prevalence patterns included effects of location, sex, and age, and they showed a temporal trend. Three of these models (models 17, 20, and 19), which accounted for 73% of the model weight, included a nonlinear temporal trend. Model-averaged prevalence estimates reflected this nonlinear increase among males (Fig. 3) (female data not shown) and also revealed generally higher prevalence on winter ranges as compared to corresponding GMUs (Figs. 2a, 3) and in the northern winter ranges (Fig. 3a) as compared to the central (Fig. 3b) or southern (Fig. 3c) ranges, with the

TABLE 2. Ranking of a priori (models 1–16) and post hoc (models 17–21) hypothesized models evaluating likely sex, age, and temporal influences on prevalence of chronic wasting disease (CWD) at the spatial scale of game management units (GMU).[a]

Model structure[b]	Model[c]	K[d]	AICc	ΔAICc	$\hat{w}_m$
GMU+age+(sex×trend^2)	20	10	3,301.0	0.0	0.55
GMU+sex+age+trend^2	17	9	3,303.3	2.3	0.17
GMU+sex+age+trend	15	9	3,304.1	3.2	0.11
GMU+sex+(age×trend^2)	19	10	3,305.2	4.3	0.06
GMU+(sex×age×trend^2)	18	13	3,305.5	4.5	0.06
GMU+sex+age+time	16	14	3,306.3	5.4	0.04
GMU+age+(sex×time)	21	20	3,310.7	9.8	0.00
GMU+age+trend	11	8	3,346.3	45.3	0.00
GMU+age+time	14	13	3,347.1	46.1	0.00
(GMU+age)×trend	12	14	3,352.0	51.0	0.00
GMU+sex+trend	6	8	3,353.7	52.7	0.00
(GMU+sex)×trend	7	14	3,355.6	54.7	0.00
GMU+sex+time	10	13	3,356.6	55.7	0.00
GMU×age×trend	13	23	3,359.0	58.0	0.00
GMU+sex	2	7	3,361.8	60.8	0.00
GMU×sex×trend	8	23	3,363.9	62.9	0.00
GMU×sex	3	12	3,369.0	68.1	0.00
GMU+trend	4	7	3,388.1	87.1	0.00

[a] Data were from yearling and adult mule deer sampled in northcentral Colorado, USA, September 1996–April 2003. Models were ranked by AICc values and normalized AICc weights ($\hat{w}_m$). See Table 1 for detailed model descriptions and genesis.
[b] Trend = linear trend over time ("trend"); trend^2 = quadratic trend over time; time = year-to-year variation in prevalence without a clear trend, modeled as a categorical variable.
[c] Model numbers correspond to those in Table 1. Models 8 and 13 did not converge.
[d] Number of estimable parameters.

exception of the Masonville winter range (Fig. 3c).

Demographic patterns from cementum annuli data

Data from 1,772 age-classified mule deer, including 290 CWD-positive (16.4%) individuals, were included in the subsample of mule deer with age determined by tooth cementum. Based on AICc, the model that incorporated 10 age classes best fit these data; the model with five age classes, although plausible, was 1.92 ΔAICc units lower. Consequently, we performed chi-square analyses and estimated prevalence by sex for the 10 age classes, excluding yearlings, because they were not tooth-aged and, thus, could introduce bias. Disease status (positive or negative) was not independent of age for males (n = 285, df = 6, χ^2 = 18.4, P = 0.005) or females (n = 387, df = 8, χ^2 = 17.2, P = 0.028) (Fig. 4). In general, the lack of independence for males came from the 2-, the 5- to 6-, and the 8-yr age classes: More negatives than expected were found among 2- and 8-yr-old males, and more positives than expected were found among 5- and 6-yr-old males (Fig. 4a). For females, the 2- and 10-yr age classes showed a proportionally large contribution to the lack of independence: More positives than expected were found among 2-yr-old females, and fewer positives than expected were found among ≥10-yr-old females (Fig. 4b).

Prevalence trends varied by sex and age; the model best representing these trends was a humped model, with sex effects being multiplicative with age and age^2 (Fig. 5). This top model was 24.2 ΔAICc units higher than the next best model (a humped model, with sex effects being additive with age and age^2) and 96.2 ΔAICc units higher than the null model (i.e., no age-specific trends in prevalence for males or females). For males, prevalence increased and then declined with age, peak-

TABLE 3. Ranking of a priori (models 1–16) and post hoc (models 17–21) hypothesized models evaluating likely sex, age, and temporal influences on prevalence of chronic wasting disease (CWD) at the spatial scale of winter ranges.[a]

Model structure[b]	Model[c]	K[d]	AICc	ΔAICc	$\hat{w}_m$
Winter range+sex+age+trend^2	17	15	970.7	0.0	0.36
Winter range+sex+age+trend	15	15	971.7	1.0	0.22
Winter range+age+(sex×trend^2)	20	16	971.8	1.1	0.21
Winter range+sex+(age×trend^2)	19	16	972.4	1.7	0.16
Winter range+(sex×age×trend^2)	18	19	975.1	4.4	0.04
Winter range+sex+age+time	16	19	976.7	6.0	0.02
Winter range+age+(sex×time)	21	24	984.1	13.4	0.00
Winter range+sex+trend	6	14	985.8	15.1	0.00
Winter range+sex+time	10	18	991.0	20.3	0.00
Winter range+age+trend	11	14	991.1	20.4	0.00
Winter range+age+time	14	18	994.6	23.9	0.00
(Winter range+sex)×trend	7	26	1,000.1	29.4	0.00
Winter range+trend	4	13	1,001.0	30.3	0.00
Winter range+sex	2	13	1,004.5	33.9	0.00
Winter range+time	9	17	1,004.8	34.1	0.00
(Winter range+age)×trend	12	26	1,006.8	36.1	0.00
Winter range;×age×trend	13	35	1,007.1	36.4	0.00
Winter range×sex×trend	8	45	1,008.8	38.1	0.00
Winter range	1	12	1,012.3	41.6	0.00
Winter range×trend	5	24	1,015.2	44.5	0.00
Winter range×sex	3	24	1,015.4	44.7	0.00

[a] Data were from yearling and adult mule deer sampled in northcentral Colorado, USA, September 1996–April 2003. Models were ranked by AICc values and normalized AICc weights ($\hat{w}_m$). See Table 1 for detailed model descriptions and genesis.
[b] Trend = linear trend over time ("trend"); trend^2 = quadratic trend over time; time = year-to-year variation in prevalence without a clear trend, modeled as a categorical variable.
[c] Model numbers correspond to those in Table 1. Models 8 and 13 did not converge.
[d] Number of estimable parameters.

ing in the 6-yr age class (29.7%, 95% CI = 1.2–58.2). The largest increase occurred between the 4- and 5-yr age classes, and the largest decrease occurred between the 6- and 7-yr age classes (Fig. 5a): Prevalence rose from 11.6% (95% CI = 7.5–15.7) among 4-yr-old males to 20.2% (95% CI = 8.6–31.7) among 5-yr-old males (P = 0.003) and decreased from 29.7% (95% CI = 1.2–58.2) among 6-yr-old males to 13.3% (95% CI = 0–29.5) among 7-yr-old males (P = 0.025). Female prevalence did not show a clear, nonlinear pattern (hence the sex×age^2 interaction in the top model): Age-specific prevalence ranged from 2.2–9% for 1- to 9-yr-old females and averaged 5.5% (95% CI = 4.7–6.3); prevalence also tended to decline in older females (1.1% among ≥10-yr-old females) (Fig. 5b). With the exception of the 1- to 2-yr age classes, the prevalence among males was higher than the prevalence among females for all other comparable age classifications (3- to 7-yr age classes). On average, male prevalence was 2.4-fold higher than female prevalence for the 3- to 7-yr age classes ($P \leq 0.004$ for all within-age class comparisons) (Fig. 5a, b). The difference was especially pronounced for the 5- to 7-yr age classes, in which prevalence among males was 3.8-fold higher than that among females.

DISCUSSION

Demographic, spatial, and temporal factors all appear to contribute to the marked heterogeneity in CWD prevalence observed at several levels of geographic resolution in endemic portions of northcentral Colorado (Miller et al., 2000; Wolfe et al., 2002; Conner and Miller, 2004). These factors likely combine in various ways to

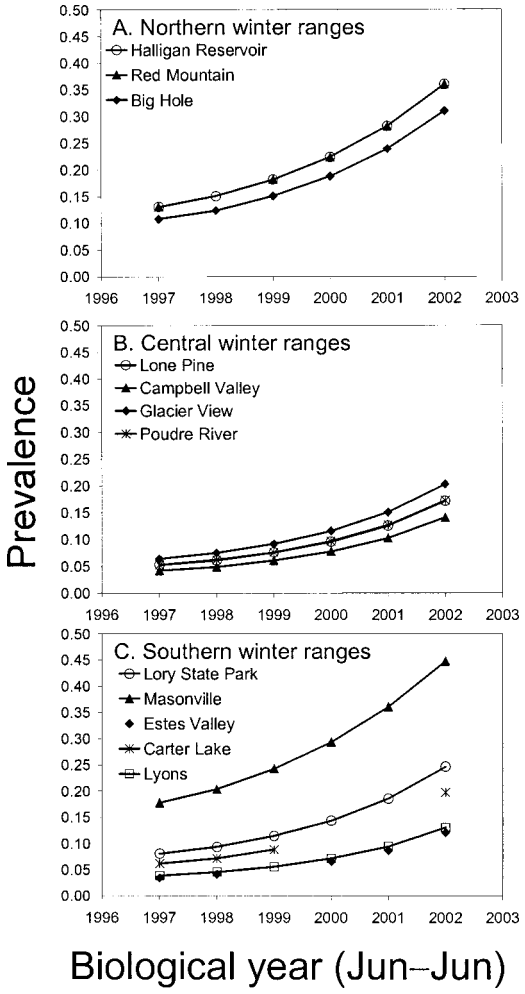

FIGURE 3. Model-averaged predicted values of chronic wasting disease (CWD) prevalence among adult male mule deer in northcentral Colorado, USA, versus biological year for (A) northern, (B) central, and (C) southern winter ranges as shown in Figure 1 (September 1996–April 2003). A biological year was defined as 15 June–14 June.

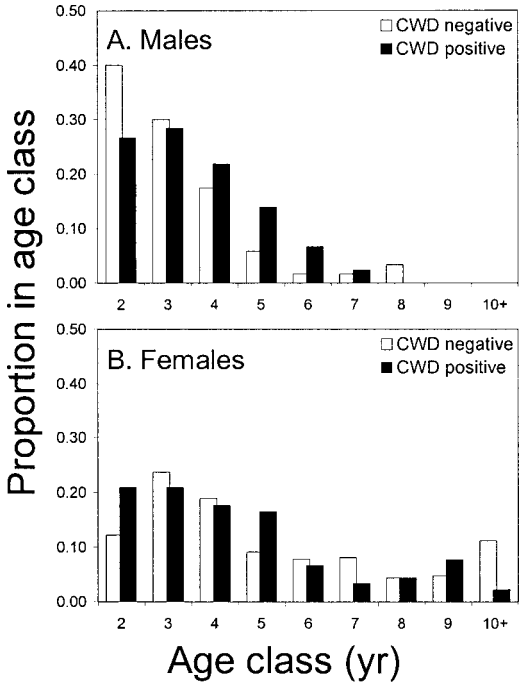

FIGURE 4. Age distributions of chronic wasting disease (CWD)–infected mule deer as compared to age distributions of uninfected deer separated by sex: (A) proportion of total negative or positive males in each age class, and (B) proportion of total negative or positive females in each age class. Proportions were estimated from a subset of field data from mule deer harvested or culled (September 1996–April 2002) in northcentral Colorado, USA, with age determined via tooth cementum annuli.

influence epidemic dynamics on both local and broad geographic scales. Observed heterogeneity in CWD prevalence across landscapes is consistent with the notion that endemic CWD arises from epidemics on a protracted time scale (Miller et al., 2000). It follows that patterns discerned from point estimates or short-term studies like ours would be the product of these and, perhaps, other as-yet-unidentified factors. Understanding the relative importance and exploitability of such factors seems to be key in forecasting epidemic trends and designing control strategies.

Prevalence of CWD was higher for male mule deer for every age class except the 1–2 yr olds; for the 3- to 7-yr age classes, prevalence was 2.4-fold higher among males than among females (Fig. 5), with differences being especially pronounced in the 5- to 6-yr age classes. Markedly higher prevalence among 5- to 6-yr-old males likely contributed to the observed higher prevalence among males at both geographic scales studied here as well as in the urban Estes Park mule deer herd, in which CWD prevalence among adult males was threefold higher than that among sympatric adult females (Wolfe et al., 2004). Dif-

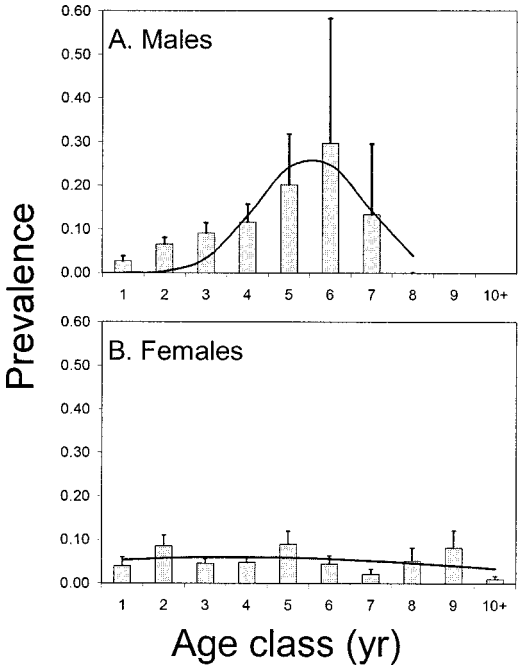

FIGURE 5. Age class-specific estimates of chronic wasting disease (CWD) prevalence for a sample of (A) male and (B) female mule deer harvested or culled (September 1996–April 2002) in northcentral Colorado, USA. Error bars represent 95% confidence intervals for estimated prevalence. Curves are predicted values from the trend model best fitting these data (model = sex+age+age^2+sex×age+sex×age^2).

ferences in CWD prevalence between sexes stands in contrast to observations that captive male and female mule deer appear to be equally susceptible to infection (Williams and Young, 1980, 1992; Williams and Miller, 2002; Miller and Wild, 2004; Miller et al., 2004). Higher CWD prevalence among males than among sympatric females also has been observed in mule deer in southeastern Wyoming (Kreeger, pers. comm.), in white-tailed deer in Wisconsin (Grear et al., 2005), and in wapiti in northcentral Colorado (Miller and Conner, unpubl.), suggesting that common transmission mechanisms and contact structures among the three natural host species may drive epidemic dynamics.

In addition to the large difference in prevalence between prime-aged male and female mule deer, we also observed a large difference in prevalence among males between age classes. Prevalence among 5- to 7-yr-old male deer was 1.7- to 3.2-fold higher than prevalence among males in younger age classes. This pattern of relatively high prevalence among mature males was similar to that reported in a previous study (Miller et al., 2000) that presented a subset of the data analyzed here. Although no definite pattern in prevalence was observed across age classes for females, our data reflected a more generalized age-related trend: For both sexes, risk of infection appeared to increase in early adulthood, resulting in relatively high prevalence in adult (≥2-yr-old) mule deer as compared to yearlings. However, whether this pattern arises from cumulative exposure to CWD agent over time or from age-related changes in susceptibility remains to be determined. The trends we observed across younger age classes resembled those reported by O'Brien et al. (2002) for rates of *Mycobacterium bovis* infections across white-tailed deer age classes. Differences in patterns among older age classes (declining CWD prevalence in oldest age classes and sustained bovine tuberculosis prevalence in oldest age classes) most likely reflect differences in disease-caused mortality rates. Because the clinical course of CWD is relatively short compared to that of bovine tuberculosis and deer life span, CWD would not be expected to accumulate in older age classes. Alternatively, patterns in CWD prevalence could be a result of age-related decline in either susceptibility or exposure risk. Because CWD and bovine tuberculosis in deer share several important epidemiological features (e.g., direct and indirect horizontal transmission, prolonged incubation, little if any acquired resistance or "herd immunity"), it seems likely that biologic and ecologic processes common to white-tailed and mule deer underlie these patterns.

The mechanism driving remarkably high CWD prevalence among prime-aged, male mule deer remains uncertain. Gender-related differences in prevalence may be

produced by social or foraging behaviors, movements, or some other process that differentially increases male exposure to the CWD agent. Breeding and attendant social behaviors vary in several respects between male and female mule deer, and these differences may explain higher CWD prevalence in older males. Sexually mature (>2-yr-old) male mule deer roam widely during the breeding season (Geist, 1981), and higher prevalence among mature males could simply reflect increased probability of males interacting with sources of infection by associating with numerous different females or by fighting with other males (Koutnik, 1981). Because female mule deer clans may be facultatively territorial and, thus, intermix much less often (Geist, 1981), the probability of individual females interacting with sources of infection would be expected to be lower than the average male's, unless CWD was introduced into the home range of an individual female's clan. During the rut, male mule deer stimulate females to urinate, thereby allowing males to identify females in estrus (Estes, 1972). Rutting males canvass as many females as possible (Kucera, 1978; Geist, 1981), smelling and licking the vulva and perineum of females (Kucera, 1978; Geist, 1981). Because courtship in mule deer is often protracted (Geist, 1981), such contacts likely occur repeatedly during the breeding season. If CWD is transmitted via excreta (Williams and Miller, 2002; Miller and Williams, 2003), then these behaviors also may increase exposure risk in male mule deer. Alternatively, some other process related to sex-specific susceptibility, behavior, or ecology (e.g., habitat selection, home range size, diet selection) could underlie the pattern we observed. For example, older male mule deer may withdraw to relatively isolated winter and summer ranges with a few companion "bachelors," and transmission within these bachelor groups also could account for the patterns we observed: CWD-infected pairs or trios of male mule deer have been documented in field studies (Wolfe and Miller, unpubl.). The observed prevalence pattern among male age classes suggests that exposure risk may be greatest in adulthood, perhaps because males interact with more groups or roam more widely while seeking to establish social dominance. A similar pattern of higher prevalence of bovine tuberculosis among male white-tailed deer was attributed to biologic and behavioral influences, particularly male dispersal and sex-specific social interactions (O'Brien et al., 2002).

Deeper understanding of the processes that give rise to sex- and age-related variation in prevalence could aid in developing effective control strategies for CWD and, perhaps, other infectious diseases of deer and closely related cervids. The patterns observed here suggest that mule deer populations infected with CWD should be managed to produce relatively young age structures in areas where disease control is a desired management outcome. Emergence of CWD in northcentral Colorado during the last two decades has coincided with a nearly 80% reduction in annual harvest of male mule deer between 1984 and 1998 (CDOW, unpubl.); female harvest also remained conservative during this period. Whether more liberal harvest and culling regimens imposed since 2001 will reduce CWD prevalence remains to be determined. Although preliminary analyses of recent prevalence trends show some indication that such approaches may be damping increases in prevalence (Miller and Conner, unpubl.), changing host age structure could simply shift infection to younger age classes if CWD transmission is not somehow interrupted by harvest and culling. Observed differences in prevalence between males and females suggest potential merit in sex-specific CWD management strategies. In light of these trends and uncertainties, controlled field experiments evaluating the efficacy of population management in controlling CWD clearly are warranted. Moreover, because prime-aged male deer (and wapiti) are more like-

ly than other sex-age classes to be processed as trophy mounts, our data suggest that taxidermy facilities could represent points of concentration for handling CWD-infected animals. It follows that taxidermy facilities may be useful contact points for collecting samples for CWD surveillance and that, perhaps, the distribution of such facilities (as well as game processing facilities) should be factored into future geographic assessments of CWD risk.

Prevalence of CWD varied across our study area at both coarse and fine scales of resolution. Prevalence was higher among samples collected on winter ranges than among samples collected throughout corresponding GMUs. This observation may be, in part, an artifact of focusing previous studies of mule deer movements (Conner and Miller, 2004) in areas where prevalence was perceived to be relatively high and, thus, selectively defining some of the winter ranges associated with these high prevalence areas and, perhaps, missing others with lower prevalence. Even taking into account this potential bias, however, prevalence seemed to be higher on defined winter ranges within a GMU than for the GMU as a whole. The explanation for this pattern is unclear. Although the combined effects of accumulated residual excreta and decomposed carcasses (Miller et al., 2004) and the relatively sedentary behavior of deer (Geist, 1981; Conner and Miller, 2004) on winter ranges could foster local transmission, we would not expect to detect such strong spatial relationships from deer harvested before the fall migration was complete. If this pattern is not a sampling or analysis artifact, then we can only surmise that mule deer harvested on winter ranges in our study area may differ from deer harvested away from recognized winter ranges in some manner (e.g., movement, social behavior, or exposure risk) that we did not measure. Regardless of the ultimate explanation, our data suggest that areas where deer congregate seasonally may be particularly important in sustaining CWD epidemics in free-ranging populations and, thus, may serve as targets for both surveillance and management.

Our analyses demonstrated that coarse-scale evaluations using GMUs as spatial units, although perhaps convenient for historical and public information purposes, were not particularly informative. Because mule deer movements and, likely, other important features of mule deer ecology in our study area operated independent of these artificial landscape units, biologically defined population units appeared to be a more useful denomination for studying the spatial epidemiology of CWD (Conner and Miller, 2004). Prevalence varied considerably among sampled winter ranges, generally declining from north to south (Fig. 3); exceptions to this general trend supported the notion (Conner and Miller, 2004) that simple diffusion models may not represent faithfully the mechanisms for geographic spread of CWD among mule deer in northcentral Colorado. Whether differences in habitat or movement patterns among winter ranges contributed to heterogeneity or such differences simply reflect a legacy effect arising from different durations of local epidemics remains to be investigated.

In contrast to strong demographic and spatial trends in CWD prevalence, temporal trends were somewhat less pronounced in our data. Although seven consecutive years of data may be sufficient to study dynamics of many infectious diseases in natural populations, our study period covered a relatively small fraction of the protracted timelines thought to be characteristic of CWD epidemics (Miller et al., 2000; Gross and Miller, 2001). The plodding pace of CWD epidemic dynamics, combined with the relative scarcity of CWD in affected populations, greatly complicates reliable analysis of prevalence trends. We found stronger evidence for a nonlinear increase in CWD prevalence through time in data from male mule deer at both geographic scales. Females did not

show the same strong, increasing trend in CWD prevalence through time; this may be attributable to small sample sizes, lower prevalence, or lower prevalence coupled with some biologic mechanism or factor that dampens epidemic dynamics in the female segment of affected mule deer populations. In light of these findings, it appears that monitoring male mule deer may be the most reliable approach for discerning short-term temporal trends in CWD prevalence because of larger sample sizes and higher relative prevalence; however, understanding trends in female segments of affected populations will be more important in assessing the long-term impacts of CWD. Effects of CWD on mule deer population performance remain to be determined. Of perhaps greatest importance in terms of implications for affected mule deer populations, sampled population units studied here showed increasing prevalence trends that in several of the northern winter ranges (Fig. 3a) were similar to trends observed in captive populations of mule deer (Miller and Williams, 2003) and white-tailed deer (Miller and Wild, 2004) naturally infected with CWD.

In an attempt to reconcile data presented here with previous observations, we offer a conceptual model of the spatiotemporal dynamics of CWD in northcentral Colorado mule deer herds. We envision "endemic CWD" as an aggregation of interrelated, but largely independent, local epidemics. These epidemics probably have followed general dynamic patterns described by both empiric and modeled data (e.g., Miller et al., 2000; Gross and Miller, 2001; Miller and Williams, 2003) but began at different times over the last 25 or more years. The basic demographic units for epidemic dynamics are relatively insular, female, matriarchal clans. Male mule deer may interact with numerous clans during breeding, thus increasing opportunities for exposure and attendant risk of infection in males; interactions within small bachelor groups of males also may contribute to higher risk among adult males. By virtue of their higher infection rates, infected male mule deer may be more responsible than infected females for local spread of CWD within a population unit. Probabilistic interactions of mule deer population units likely have driven the overall pace and pattern of larger-scale geographic spread (Conner and Miller, 2004). Local conditions, both natural and anthropogenic, may have influenced CWD transmission or persistence (Miller et al., 2000; Gross and Miller, 2001; Williams and Miller, 2002; Wolfe et al., 2002, 2004; Farnsworth et al., 2005) and further confounded the spatial heterogeneity produced by the staggered start and complex geographic spread of local epidemics.

In the context of these concurrent but asynchronous epidemics playing out over several decades, the data presented here constitute a temporal snapshot that yielded cross-sections of numerous local, ongoing CWD epidemics in northcentral Colorado mule deer herds. Areas of relatively low prevalence may be places where CWD has been introduced relatively recently, and areas with higher prevalence represent longer-standing epidemics. The foregoing assumptions can be formulated into hypotheses that are testable under the model selection approaches used here, and such analyses warrant further consideration. A more comprehensive understanding of CWD epidemiology, including both roles and interactions of demographic, spatial, and temporal factors, is needed to assess the implications of, and to craft management strategies for, this emerging wildlife health problem.

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