EPIZOOTIOLOGY OF CHRONIC WASTING DISEASE IN FREE-RANGING CERVIDS IN COLORADO AND WYOMING

MICHAEL W. MILLER, ELIZABETH S. WILLIAMS, CRAIG W. MCCARTY, TERRY R. SPRAKER, TERRY J. KREEGER, CATHERINE T. LARSEN, AND E. TOM THORNE

Made in United States of America
Reprinted from JOURNAL OF WILDLIFE DISEASES
Vol. 36, No. 4, October 2000

Journal of Wildlife Diseases, 36(4), 2000, pp. 676–690

EPIZOOTIOLOGY OF CHRONIC WASTING DISEASE IN FREE-RANGING CERVIDS IN COLORADO AND WYOMING

Michael W. Miller,[1,8] Elizabeth S. Williams,[2] Craig W. McCarty,[3,7] Terry R. Spraker,[4] Terry J. Kreeger,[5] Catherine T. Larsen,[1] and E. Tom Thorne[6]

[1] Colorado Division of Wildlife, Wildlife Research Center, 317 West Prospect Road, Fort Collins, Colorado 80526-2097, USA

[2] Department of Veterinary Sciences, University of Wyoming, 1174 Snowy Range Road, Laramie, Wyoming 82070, USA

[3] Graduate Degree Program in Ecology, Colorado State University, Fort Collins, Colorado 80523, USA

[4] Colorado State Diagnostic Laboratory, Colorado State University, Fort Collins, Colorado 80523, USA

[5] Wyoming Game and Fish Department, 2362 Highway 34, Wheatland, Wyoming 82006, USA

[6] Wyoming Game and Fish Department, 5400 Bishop Boulevard, Cheyenne, Wyoming 82006, USA

[7] Present address: Windward Islands Research and Education Foundation, Saint George's University School of Medicine, Grenada, West Indies

[8] Corresponding author (e-mail: mike.miller@state.co.us)

ABSTRACT: Surveillance and epidemic modeling were used to study chronic wasting disease (CWD), a transmissible spongiform encephalopathy that occurs naturally among sympatric, free-ranging deer (*Odocoileus* spp.) and Rocky Mountain elk (*Cervus elaphus nelsoni*) populations in contiguous portions of northeastern Colorado and southeastern Wyoming (USA). We used clinical case submissions to identify endemic areas, then used immunohistochemistry to detect CWD-infected individuals among 5,513 deer and elk sampled via geographically-focused random surveys. Estimated overall prevalence (prevalence, 95% confidence interval) in mule deer (4.9%, 4.1 to 5.7%) was higher than in white-tailed deer (2.1%, 0.5 to 3.4%) or elk (0.5%, 0.001 to 1%) in endemic areas; CWD was not detected in outlying portions of either state. Within species, CWD prevalence varied widely among biologically- or geographically-segregated subpopulations within the 38,137 km^2 endemic area but appeared stable over a 3-yr period. The number of clinical CWD cases submitted from an area was a poor predictor of local CWD prevalence, and prevalence was typically ≥1% before clinical cases were first detected in most areas. Under plausible transmission assumptions that mimicked field data, prevalence in epidemic models reached about 1% in 15 to 20 yr and about 15% in 37 to 50 yr. Models forecast population declines once prevalence exceeded about 5%. Both field and model data supported the importance of lateral transmission in CWD dynamics. Based on prevalence, spatial distribution, and modeling, we suggest CWD has been occurring in northeastern Colorado and southeastern Wyoming for >30 yr, and may be best represented as an epizootic with a protracted time-scale.

Key words: *Cervus elaphus nelsoni*, chronic wasting disease, epidemic modeling, epizootiology (epidemiology), mule deer, *Odocoileus hemionus*, *Odocoileus virginianus*, prion, Rocky Mountain elk, transmissible spongiform encephalopathy, wapiti, white-tailed deer.

INTRODUCTION

Chronic wasting disease (CWD) is a naturally-occurring transmissible spongiform encephalopathy (TSE) of native North American deer (*Odocoileus* spp.) and Rocky Mountain elk (*Cervus elaphus nelsoni*) characterized by behavioral changes and progressive loss of body condition that are products of an invariably fatal neurodegenerative process (Williams and Young, 1980, 1982, 1992; Spraker et al., 1997). Origin and mode(s) of transmission are poorly understood. As with other TSEs of domestic animals (scrapie, bovine spongiform encephalopathy [BSE], transmissible mink encephalopathy) and humans (kuru, classic Creutzfeldt-Jacob disease [CJD], and variant CJD [vCJD]), the causative agent of CWD has not been definitively identified. However, microscopic accumulations of proteinase-resistant prion protein (PrP^{res}) in brain tissue are consistently associated with clinical disease. Chronic wasting disease appears to be novel among known TSEs: strain typing has demonstrated differences between CWD and other animal or human TSEs (Bruce et al., 1997), and natural transmission of TSEs between domestic bovids and cervids has not been documented.

Chronic wasting disease is perhaps most unique among animal TSEs in that it occurs in a few sympatric free-ranging populations of deer and elk. The only known endemic focus in free-ranging cervids spans contiguous portions of northeastern Colorado and southeastern Wyoming (USA). Here we report analyses and syntheses of preliminary epidemiological data gathered from free-ranging cervid populations infected with CWD. Our specific objectives were to estimate prevalence and assess recent temporal trends, to evaluate spatial and demographic attributes of endemic CWD, and to use surveillance data in parameterizing and evaluating simple models developed to forecast temporal dynamics and impacts on affected populations.

MATERIALS AND METHODS

Study area

The primary focus of our study was a 38,137 km^2 polygon in southeastern Wyoming and northeastern Colorado where CWD is endemic in free-ranging cervids (Fig. 1A). This endemic area is bounded largely by the North and South Platte rivers. About 62,000 deer (mostly mule deer; *O. hemionus*) and 13,200 elk are distributed among numerous resident subpopulations (Colorado Division of Wildlife [CDOW], unpubl. data; Wyoming Game and Fish Department [WGFD], unpubl. data). Within this area, deer and elk habitats range from alpine and coniferous mountain shrub types in western portions to riparian corridors and shortgrass prairie tablelands in eastern portions; agricultural and suburban developments are intermixed with native habitats throughout. Mule deer predominate in the western mountains and foothills, but are less abundant in the eastern tablelands and riparian areas; conversely, white-tailed deer (*O. virginianus*) are far more abundant in eastern riparian corridors and associated tablelands than in the mountains and foothills. Elk are largely restricted to the mountains and foothills. Low animal densities, adequate winter range, and limited snowfall have historically allowed deer and elk populations to be managed without supplemental feeding throughout the endemic area.

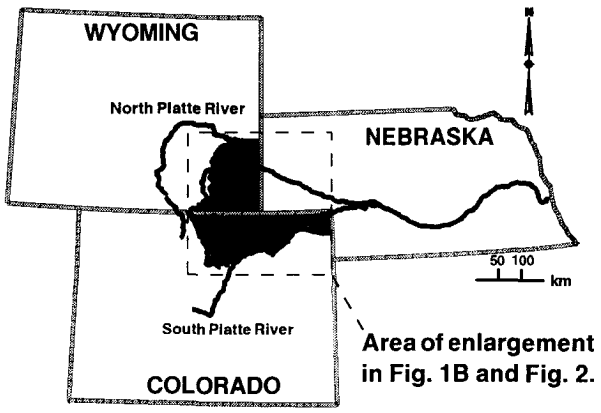
For epidemiological investigations, we collected samples from management units (MUs) within (Fig. 1B) and outside CWD-endemic portions of both Colorado and Wyoming. These MUs have been established by respective state wildlife management agencies to aid in population management and law enforcement; boundaries are typically established with more regard for simplicity in recognition and description than for biological relevance. Consequently, we used MUs here only as a means for describing the approximate geographic origins of clinical suspects and harvested animals in order to assess spatial features of CWD epidemiology.

Trageted surveillance

Between 1978 and 1999, 358 "suspect" deer and elk showing clinical signs consistent with CWD (≥1.5 yr old, poor body condition, abnormal behavior, ± other signs) (Williams and Young, 1980, 1982, 1992; Spraker et al., 1997) were collected. Of these clinical suspects, 168 deer and 63 elk came from within the endemic area and 89 deer and 38 elk came from outlying parts of both states. Complete necropsies were performed in most cases and select tissues, including brainstem, were preserved in 10% neutral phosphate-buffered formalin.

In all cases, histopathology of brain tissue with particular attention to the medulla oblongata at the obex was used to diagnose CWD (Williams and Young, 1993; Spraker et al., 1997). Tissues were sectioned at 5 to 6 μm and stained with hematoxylin and eosin. Lesions were compared to those described for CWD in mule deer, white-tailed deer, elk, and other natural TSEs of animals (Williams and Young, 1993; Hadlow, 1996; Spraker et al., 1997).

In 37 cases, we used immunohistochemistry (IHC) to augment or confirm CWD diagnoses. Briefly, formalin-fixed, paraffin-embedded tissues were sectioned, processed and stained using minor modifications of techniques described previously (Miller et al., 1993; van Keulen et al., 1995). Techniques for IHC have been modified over time, but generally followed those briefly described below. We used polyclonal antiserum against mouse-passaged scrapie (Rubenstein et al., 1986; Spraker et al., 1997) or mouse monoclonal antibody (MAb) against bovine PrP (F89/160.1.5; USDA/ARS, Pullman, Washington) (O'Rourke et al., 1998). Prior to immunostaining, sections were immersed in 99% formic acid for 30 to 60 min followed by hydrated autoclaving for 10 to 20 min. Sections were immunostained with diluted primary antibody for 0.5 to 1 hr at 37 C, a biotinylated anti-rabbit or anti-mouse secondary antibody as appropriate, an ABC reagent (Vectastain ABC Kit, Vector Laboratories, Burlingame, California, USA) or alkaline phosphate strepavidin conjugate, a substrate chromagen (fast red or AEC), and a hematoxylin



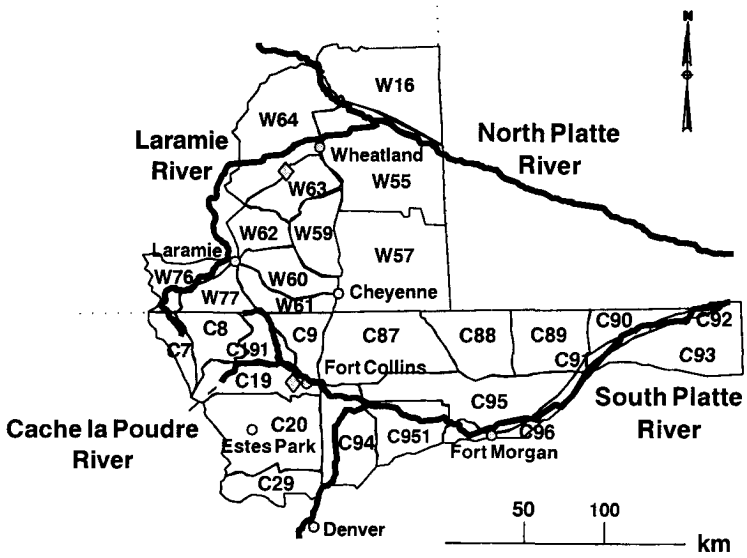


FIGURE 1. Chronic wasting disease surveillance was conducted throughout Wyoming and Colorado (USA). A. Chronic wasting disease is endemic in portions of southeastern Wyoming and northeastern Colorado. B. The endemic area is comprised of 29 management units (MUs) established by respective state wildlife management agencies to aid in deer and elk population management.

counterstain. Positive and negative brain sections, normal rabbit or mouse serum, and PBS were used as controls.

Population surveys

We surveyed select deer and elk populations (Table 1) to obtain relatively unbiased estimates of CWD prevalence and assess short-term trends. Surveys began in 1983 in Wyoming and in 1990 in Colorado, but small sample sizes and unavailability of IHC limited the value of data gathered prior to 1995; consequently, only data collected since 1996 were analyzed here.

During October 1996 to January 1999, portions of medulla oblongata were collected from 2,726 mule deer, 341 white-tailed deer, and 929

TABLE 1. Estimated mean chronic wasting disease prevalence (%) and sample sizes by host species and area in southeastern Wyoming and northeastern Colorado during 1996 to 1999, as measured via population surveys.

	Mule deer		White-tailed deer		Elk	
Aggregated MUs[a]	Prevalence[b] (IHC+/total)	95% CI	Prevalence (IHC+/total)	95% CI	Prevalence (IHC+/total)	95% CI
W16, W55	4.1 (5/123)	1.3–9.2	15.4 (2/13)	1.9–45.6	ns[c]	nd[d]
W64	13.1 (18/137)	8.0–20.0	3.6 (1/28)	0.1–18.3	ns	nd
W59, W60, W62, W63	12.4 (11/89)	6.4–21.0	ns	nd	ns	nd
W76, W77, C7, C8	1.3 (4/311)	0.4–3.3	ns	nd	0 (0–290)	0–1.3
W61, C9	14.7 (20/136)	9.3–21.8	ns	nd	0 (0/9)	0–33.6
W57, C87, C88, C90	0.9 (1/110)	0.02–4.9	0 (0/7)	0–41.0	ns	nd
C191, C19	5.7 (39/685)	4.1–7.7	0 (0/11)	0–28.5	0.5 (1/201)	0.01–2.7
C20, C29	3.5 (27/776)	2.3–5.0	22.2 (2/9)	2.8–60.1	0.9 (4/429)	0.3–2.4
C94, C95, C951, C96	2.7 (9/331)	1.3–5.1	0.7 (1/146)	0.01–3.7	ns	nd
C90, C91, C92, C93	0 (0/138)	0–2.6	0.8 (1/129)	0.02–4.3	ns	nd

[a] Management unit aggregations based on geographic proximity and biological interrelationships (see text and Figs. 1–2).
[b] Prevalence expressed as (number of immunohistochemistry-positive samples/total)*100.
[c] Species either not harvested or, in a few cases, not sampled in this area.
[d] Not determined.

elk harvested, randomly culled, or road-killed in 29 MUs (Fig. 1B) within or adjacent to the endemic foci identified via targeted surveillance; 757 deer and 760 elk from other MU's throughout Colorado and Wyoming also were sampled. Species, sex, and MU of origin were recorded. All deer and elk included in our surveys were ≥1.3 yr old based on size and dentition. To further compare CWD occurrence across age classes and between sexes in mule deer, and to estimate age-specific prevalence rates for comparison with epidemic modeling results, ages were estimated more precisely via dentition and cementum annuli (Robinette et al., 1957; Erickson and Seigler, 1969; Larson and Taber, 1980) for all CWD-positive mule deer and a random subsample of negative mule deer (103 males and 100 females) harvested in four contiguous Colorado MUs (C9, C19, C191, C20). Age class-specific IHC-based prevalence rates were estimated for each sex; the total number of negatives in the sample for each age class was estimated from age distributions of the random subsamples of males and females. We selected these MUs because they appeared to be representative of foothills mule deer populations in the endemic area and because mule deer of both sexes had been sampled with sufficient intensity (n = 1,014 males and 485 females) to allow comparisons within and between sexes.

Formalin-fixed medulla oblongatas, sectioned at the obex, were examined for PrP^{res} accumulations by IHC (Miller et al., 1993; Spraker et al., 1997; O'Rourke et al., 1998) and lesions (Williams and Young, 1993; Spraker et al., 1997) consistent with CWD infection as described above. In these surveys, all 5,513 samples were examined by IHC; all 145 IHC-positives and about 3,000 IHC-negatives were evaluated independently by histopathology. Pathologists were blinded to samples' precise MU origins. Samples showing positive IHC reactions, with or without spongiform encephalopathy, were classified as CWD-positive. We further partitioned IHC-positives into two groups based on the presence or absence of spongiform encephalopathy. Based on our observations of CWD pathogenesis in experimentally-infected mule deer (E. S. Williams and M. W. Miller, unpubl. data), we used this ratio as a qualitative index of early versus late stages of CWD infection in assessing independent epidemic model results.

Data were analyzed using information-based model selection (Sakamoto, 1991; Burnham and Anderson, 1998). We used Akaike's information criteria corrected for small sample bias (AIC_c) for model selection and assessed goodness-of-fit using standard χ^2 approaches (Agresti, 1990; Sakamoto, 1991). Prospective models for explaining patterns in our data were confronted and compared via AIC_c to assess evidence that biologically interpretable interactions of spatial distribution, time, and/or sex influenced CWD prevalence within each host species. We analyzed the entire set of harvest-based survey data separately for each host species. Because sample sizes from harvest-based surveys were small for most individual MUs, we pooled data from adjacent MUs connected via known animal movements (Siglin, 1965; Bear, 1989; Kufeld et al., 1989; Kufeld and Bowden, 1995; CDOW, unpubl. data; WGFD, unpubl. data); specific MU aggregations are listed in Table 1. In addition, we used AIC_c to assess evidence that sex and/or age influenced CWD prevalence in mule deer data from the subset of four intensively sampled Colorado MUs (C9, C19, C191, C20). For all analyses, only information-based models with $\Delta AIC_c \leq 3$ were considered good candidates for explaining patterns in field data (Burnham and Anderson, 1998); we regarded models with $\Delta AIC_c \geq 10$ as having essentially no support in explaining such patterns. Where necessary, we constructed confidence intervals using either exact or appropriate approximation methods (Agresti and Coull, 1998).

Epidemic modeling

Based on epidemiological observations of CWD in both captive and free-ranging cervids, we constructed a simple, deterministic epidemic model to aid in evaluating some basic assumptions about CWD transmission and in forecasting CWD dynamics (both retrospective and prospective) and population impacts in mule deer.

In this model, population and disease dynamics interacted annually in discrete time. Our deer population model assumed two sexes (male, female), 13 age classes (0 to 12), and three health states (susceptible, latent, infectious). We fixed yearling and adult survival ($s_{male} = 0.4$, $s_{female} = 0.85$) and recruitment (0.57); compensatory recruitment did not occur (Bartmann et al., 1992). Under the foregoing assumptions, the population growth rate was about 6% over 50 yr when CWD was absent; this was consistent with natural growth rates estimated for healthy, low-density mule deer populations (Unsworth et al., 1999).

One modeling goal was to explore a range of plausible values for CWD transmission parameters. In our models, animal-to-animal transmission was driven by the average number of infectious contacts per infectious individual per year (β) (Heesterbeek and Roberts, 1995; McCarty and Miller, 1998). We assumed that β was density-independent. In addition to lateral transmission, we assumed that infectious females also infected their fawns at a fixed rate (P_{MAT}). Because we doubt that agent is shed uniformly throughout the disease course, we conceptually divided CWD infections in mule deer into a preinfectious latent period marked *in vivo* by initial deposition of PrP^{res} in lymphoid and brain tissues (Sigurdson et al., 1999; E. S. Williams and M. W. Miller, unpubl. data), followed by an infectious period. We assumed that the end of the latent period and initiation of agent shedding coincided with the appearance of spongiform encephalopathy and clinical signs >1 yr after infection (E. S. Williams and M. W. Miller, unpubl. data), recognizing that this may be an oversimplification of the natural disease process. Consequently, we assumed in our epidemic model that upon infection deer initially entered a noninfectious, 1-yr latent period. We modeled the probability of transition from susceptible (S) to latent (L) states ($P_{S \to L}$) as described by McCarty and Miller (1998):

$$P_{(S \to L)} = 1 - \left(1 - \frac{1}{N}\right)^{I\beta}, \qquad (1)$$

where I was the number of infectious deer, β was the average number of infectious contacts per infectious individual per unit time, and N was the total population size; in continuous time, this probability function is quantitatively similar to Heesterbeek and Roberts' (1995) representation of microparasite transmission (McCarty, 1999: Chapter 1 Appendix). Deer surviving the 1-yr latent period became infectious and remained so until death; no immunity or recovery occurred. Annual survival (s_a) of infectious deer was lowered by $s_a(0.5)^y$, where y was the number of years a deer had been infectious; infectious deer did not survive >3 time steps, and the average survival of infectious deer ($1/\lambda$) was about 1.05 yr. At the end of each time step, numbers of male and female deer in each disease state were summed across age or disease stage classes in a spreadsheet; the spreadsheet and model code are available upon written request to the senior author.

To explore potential sensitivity to variation in model parameters, we examined a number of plausible scenarios. In each case presented, we began with the introduction of one infectious female into a population of 1,000 at year 0. We

TABLE 2. Overall analyses of population survey data using Akaike's information criteria corrected for small sample bias (AIC_c) for model selection. Models with $\Delta AIC_c \leq 3$ were considered good candidates for explaining patterns in field data; models with $\Delta AIC_c \geq 10$ had essentially no support in explaining data patterns.

Species	Model (number of parameters)	ΔAIC_c	Biological interpretation
Mule deer	population (K = 10)	0 (AIC_c = 976.0)	Prevalence varies among ten biologically- and geographically-defined subpopulations within the endemic area (MU aggregates; see Table 1).
	population × sex (K = 20)	10.7	Prevalence varies between sexes and among subpopulations as defined above.
White-tailed deer	quadrant (K = 4)	0 (AIC_c = 65.2)	Prevalence varies among four broad geographic divisions of the endemic area (northern and southern foothills/mountains, northern and southern river bottoms/tablelands).
	mountains-plains (K = 2)	4.2	Prevalence varies between foothills/mountains and river bottoms/tablelands (2 broad summations of contiguous populations).
Elk	population (K = 4)	0 (AIC_c = 46.1)	Prevalence varies among four biologically- and geographically-defined populations (Table 1).
	null (K = 1)	18.1	No temporal, spatial, or intraspecific effects.

then tracked changes in total population size, as well as numbers of susceptible, latent, and infectious deer, over 50 yr under transmission scenarios that independently varied β or P_{MAT}. We compared model-generated data with independent field data, and forecast epidemic dynamics under different transmission assumptions.

RESULTS

Targeted surveillance

Since 1978, 119 CWD cases were diagnosed among 231 suspects submitted from northeastern Colorado and southeastern Wyoming. (Preliminary data from a portion of the Colorado cases included here were also reported previously by Spraker et al. [1997].) All positive cases came from MUs (n = 16) in southeastern Wyoming or northeastern Colorado (Fig. 2A–C); 79 of these cases were from two adjacent Colorado MUs (C19, C20). In all, CWD was confirmed in 84/148 mule deer, 7/20 white-tailed deer, and 28/63 elk suspects submitted from the endemic area. The first cases diagnosed in Colorado and Wyoming were in 1981 and 1985, respectively, but 109/119 clinical cases were diagnosed between 1991 and 1999. Most (82/119) CWD cases presented between November and April. None of the 127 suspects from outlying MUs was diagnosed with CWD.

Population surveys

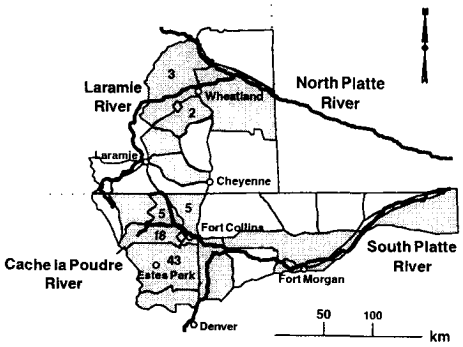
As applied here, IHC appeared to be both sensitive and specific in detecting CWD: 104 deer with histological lesions of spongiform encephalopathy tested IHC positive (lower 95% CI bound = 0.965), and all 757 deer and 760 elk from outside known endemic MUs were IHC-negative (lower 95% CI bounds ≥0.995).

Chronic wasting disease prevalence varied among the three cervid species residing in the endemic area. Overall IHC-based prevalence (prevalence, 95% confidence interval) in mule deer (4.9%, 4.1 to 5.7%) was somewhat higher than in white-tailed deer (2.1%, 0.5 to 3.4%), and much higher than in elk (0.5%, 0.001 to 1%). Only about 53% of IHC-positive mule deer and 50% of IHC-positive white-tailed deer had lesions of spongiform encephalopathy; none of the IHC-positive elk showed spongiform encephalopathy.

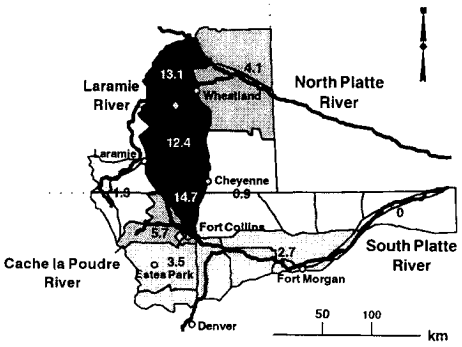
Within species, CWD prevalence varied

Mule deer

A. Number of clinical cases per MU

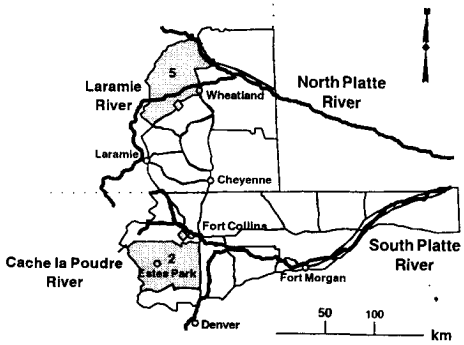


D. Estimated prevalence (%) in MU aggregates

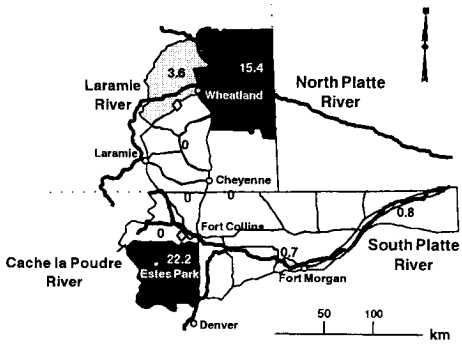


White-tailed deer

B. Number of clinical cases per MU

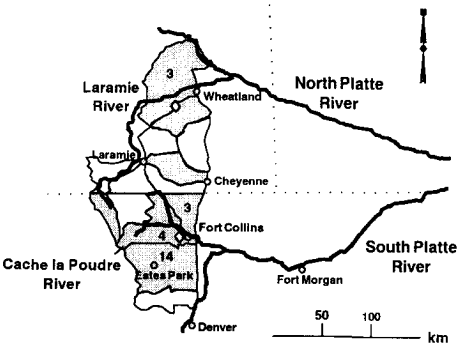


E. Estimated prevalence (%) in MU aggregate



Wapiti

C. Number of clinical cases per MU



F. Estimated prevalence (%) in MU aggregate

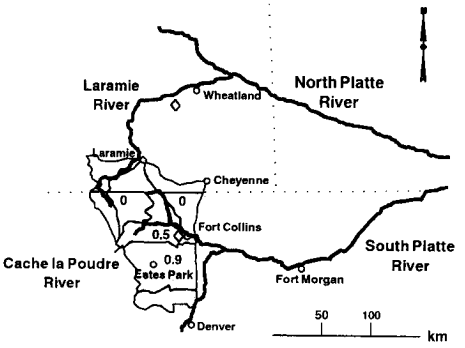


FIGURE 2. Distribution and prevalence of CWD in free-ranging cervids from endemic portions of Wyoming and Colorado, USA. The number of clinical CWD cases in (A) mule deer, (B) white-tailed deer, and

TABLE 3. Analysis of mule deer data from four Colorado MUs (C9, C19, C191, C20) using Akaike's information criteria corrected for small sample bias (AIC_c) for model selection. Models with $\Delta AIC_c \leq 3$ were considered good candidates for explaining patterns in field data; models with $\Delta AIC_c \geq 10$ had essentially no support in explaining data patterns.

Model (number of parameters)	ΔAIC_c	Biological interpretation
age × sex × disease (K = 4)	0 (AIC_c = 372.5)	Differences in distribution of CWD-positive cases between broad age groupings (≤3 yr versus ≥4 yr) within each sex (see Fig. 4).
sex × disease (K = 2)	5.7	Differences in distribution of CWD-positive cases between sexes only.
age × disease (K = 2)	26.7	Differences in distribution of CWD-positive cases between broad age groupings (≤3 yr versus ≥4 yr) only.

widely among biologically- or geographically-segregated subpopulations (Table 1, 2; Fig. 2). For mule deer, estimated mean prevalence ranged from 0 to 14.7% among MU aggregates (Table 1; Fig. 2D). This variation in prevalence tended to follow biologically-relevant spatial patterns: lower elevation foothills subpopulations at the core of the endemic area tended to be most severely affected, with prevalence declining to varying degrees in all directions (Table 2; Fig. 2D). Similar but weaker patterns were evident among white-tailed deer and elk subpopulations (Table 1, 2; Fig. 2E–F). Aside from detecting presence of CWD in most areas, local prevalence could not be predicted reliably from targeted surveillance data (Fig. 3). In contrast to strong spatial influences on CWD prevalence, temporal trends were not evident over the 3-yr survey period.

We also detected no strong tendency for CWD prevalence to differ between sexes in any of the three host species ($\Delta AIC_c \geq$ 10.7 for explanatory models that included sex as a factor; Table 2). For mule deer, comparisons of overall prevalence (prevalence, 95% confidence interval) between males (5.5%, 4.4 to 6.5%) and females (3.6%, 2.4 to 4.9%) were somewhat confounded because female mule deer were rarely harvested or sampled in Wyoming MUs; prevalence among males (6%, 4.6 to 7.5%) and females (5.2%, 3.2 to 7.1%) from four intensively sampled Colorado MUs (C9, C19, C191, C20) were more similar than in overall comparisons. Within the latter data set, we detected evidence of sex-specific differences in prevalence between broad age classes (≤3-yr-old versus ≥4-yr-old) (Table 3, Fig. 4A-B); these differences reflected, at least in part, the disparity in underlying age structures between sexes resulting from relatively unlimited annual harvest of male (but not female) mule deer in these MUs. Prevalence was also similar between male (2.3%, 0.3 to 4.6%) and female (1.4%, 0 to 3.4%)

←

(C) elk detected via targeted surveillance between 1978 and 1999 varied among species and management units (MUs). Clinically affected deer or elk were documented in 16 of the 29 MU's comprising the endemic area; unless otherwise marked, MUs shaded in (A–C) yielded only one clinical case over the last 18 years. Estimated CWD prevalence (%) in (D) mule deer, (E) white-tailed deer, and (F) elk also varied markedly among and within species across the endemic area. In general, CWD was more prevalent in mule deer than in white-tailed deer or elk. The largest and most intense focus of CWD infection spanned portions of southeastern Wyoming and northcentral Colorado, where about 12.4 to 14.7% of sampled mule deer were IHC-positive. Smaller but equally intense foci were also encountered in white-tailed deer, although prevalence estimates for these were based on relatively small sample sizes (Table 1). Diamonds near Fort Collins, Colorado and Wheatland, Wyoming mark locations of wildlife research facilities where CWD was first described.

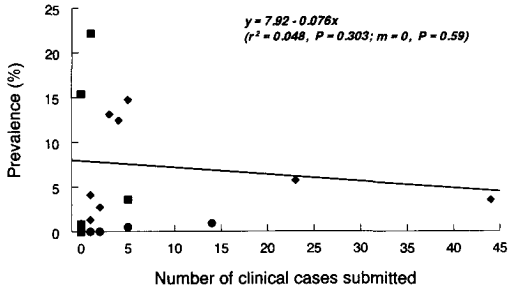


FIGURE 3. The number of clinical CWD cases submitted via targeted surveillance was poorly correlated with estimated CWD prevalence in mule deer (♦), white-tailed deer (■), and elk (●). Aside from detecting presence of CWD in most areas, local prevalence could not be predicted reliably from targeted surveillance data (r^2 = 0.048, P = 0.303; m = 0, P = 0.59).

white-tailed deer, and between male (0.7%, 0 to 1.5%) and female (0.3%, 0 to 0.9%) elk.

Epidemic modeling

Our epidemic model independently simulated field data in two important respects. First, the 1:1 ratio of latent : infectious animals produced by the model closely approximated the 1:1.13 ratio of IHC-positive : lesioned mule deer described above. Second, sex- and age class-specific prevalence patterns produced by the model (Fig. 4C–D) were remarkably similar to patterns reflected in field data (Fig. 4A–B). Based on these similarities, we regarded the model's underlying assumptions about CWD epidemiology and

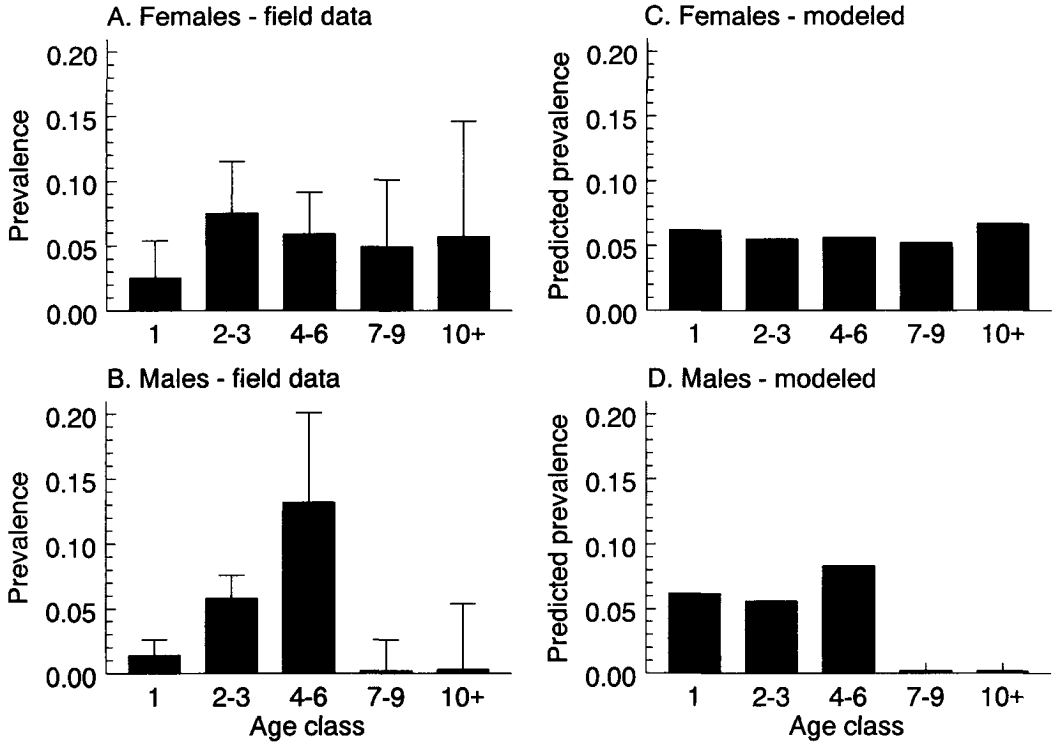


FIGURE 4. Among mule deer, we detected evidence that CWD prevalence differed between broad age classes (≤3-yr-old versus ≥4-yr-old) within each sex. Differences between age structures of (A) female and (B) male subpopulations were driven largely by liberal harvest regimes for male deer. Our epidemic model produced age class-specific prevalence patterns for (C) female and (D) male deer that were remarkably similar to patterns in field data. Field data are from mule deer harvested in four Colorado MUs (C9, C19, C20, C191); vertical lines are upper bounds of 95% confidence intervals on age class-specific prevalence estimates. Simulation data are from yr 31 (prevalence = about 5%) of a model where β = 1.25 and P_{MAT} = 0.05; see methods for other parameter assumptions.

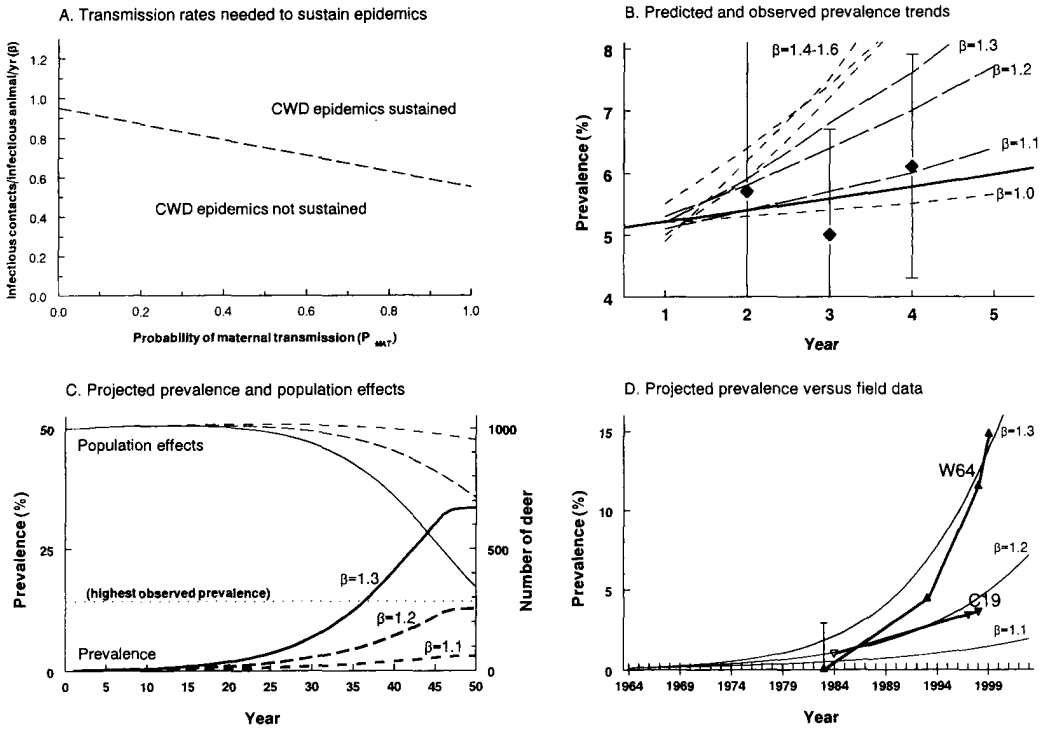


FIGURE 5. Epidemic models of CWD in mule deer. A. Modeled epidemics of CWD in mule deer were sustained by various combinations of animal-to-animal (β) and maternal (P_{MAT}) transmission values. Epidemics were sustained if $\beta \geq 0.95$ infectious contacts per infectious individual per yr, even where $P_{MAT} = 0$; in contrast, maternal transmission alone could not sustain endemic CWD. B. Models where $\beta \leq 1.1$ infectious contacts per infectious individual per yr most closely approximated nonsignificant short-term trends in field data from male mule deer, but failed to achieve overall prevalence seen in several field locations; higher transmission rates ($\beta \geq 1.4$ infectious contacts per infectious individual per yr) produced annual rates of change in prevalence (≥ 1%/yr) that rapidly exceeded rates estimated from field data. Models where $\beta = 1.2$ to 1.3 infectious contacts per infectious individual per yr produced the most plausible epidemic dynamics. C. Using $\beta = 1.2$ to 1.3 infectious contacts per infectious individual per yr, modeled epidemics reached about 1% prevalence (lower lines) in 15 to 20 yr and about 15% prevalence in 37 to 50 yr. Models forecast population declines (upper lines) once prevalence exceeded about 5%. D. These models also approximated prevalence trends for two MUs (C19, W64) where limited historical data were available. In (B), vertical lines span 95% confidence intervals on overall CWD prevalence estimates (♦) for male mule deer in 1996, 1997, and 1998; the solid line represents the best fit through these point estimates ($r^2 = 0.129$, $P = 0.148$). In (D), points (▲, ▼) are measured (or assumed for C19 in 1984; see text) prevalence estimates for MUs where data were available for >10 yr; the vertical line spans the 95% confidence interval on estimated CWD prevalence in W64 in 1983-84 (0/124, examined via histopathology only; E. S. Williams, unpubl. data).

population biology as largely consistent with the natural processes driving CWD dynamics in the mule deer populations we studied.

The model was highly sensitive to changes in β, and to a lesser extent to changes in P_{MAT}. Modeled epidemics were sustained by various combinations of lateral (β) and maternal (P_{MAT}) transmission values (Fig. 5A). However, maternal transmission alone could not sustain endemic CWD: even when $P_{MAT} = 1.0$ (its highest possible value, indicating all infectious does transmitted CWD to their fawns), CWD was eliminated unless $\beta \geq 0.55$ infectious contacts per infectious individual per yr. In contrast, CWD persisted when $\beta \geq 0.95$ infectious contacts per infectious individual per yr, regardless of P_{MAT}'s value. Based on observations of CWD epi-

demiology in captive mule deer, maternal transmission appears to be relatively rare (≤3.4% of cases; M. W. Miller, unpubl. data); consequently, we used $P_{MAT} = 0.05$ in subsequent simulations of epidemic dynamics.

When β values were adjusted to approximate field data (β = 1 to 1.3) (Fig. 5B), the estimated basic reproduction ratio (R_0) for CWD in modeled mule deer populations ranged from 1.5 to 1.95. Models where β = 1.2 to 1.3 infectious contacts per infectious individual per yr produced the most plausible dynamics (Fig. 5B–D), perhaps best described as epidemics with protracted time-scales. Although models where β ≤ 1.1 infectious contacts per infectious individual per yr most closely approximated nonsignificant short-term trends in field data from male mule deer (Fig. 5B), these models failed to achieve overall prevalence observed in six of ten MU aggregates (Fig. 5C) and underestimated trends reflected in two limited long-term data sets (Fig. 5D). When β = 1.2 to 1.3 infectious contacts per infectious individual per yr, modeled epidemics reached about 1% prevalence in 15 to 20 yr and about 15% prevalence in 37 to 50 yr (Fig. 5C). At higher transmission rates (β ≥ 1.4 infectious contacts per infectious individual per yr), annual rates of change in prevalence (≥1%/yr) rapidly exceeded rates estimated from our surveys (Fig. 5B). Models forecast population declines once prevalence exceeded about 5% (Fig. 5C).

DISCUSSION

Estimated CWD prevalences among populations we studied are higher than reported in surveys of other animal TSEs because we included preclinical (and perhaps subclinical) cases where only IHC reactions were observed. Comparable data for the other animal TSEs are not available. Epidemiological surveys of scrapie and BSE (Detwiler, 1992; Anderson et al., 1996; Hoinville, 1996; Wineland et al., 1998) typically report only clinical cases. Including preclinical and subclinical disease states more accurately estimates the true rate of infection. Reporting only clinical cases would have dramatically underestimated the true prevalence of CWD here: of 133 IHC-positive mule deer identified in our harvest surveys, only four were clinical cases (estimated mean prevalence 4.9% versus 0.1%). Only about 53% of positive mule deer showed both histopathological lesions of spongiform encephalopathy and IHC staining; the remainder were classified as positive solely on the basis of IHC. It is likely that our IHC-based prevalence estimates still underestimated true prevalence (by a factor of about 0.75 to 0.8; M. W. Miller, unpubl. data) because staining does not appear in the medulla oblongata of deer for >3 mo after infection (Sigurdson et al., 1999; E. S. Williams and M. W. Miller, unpubl. data).

The two surveillance approaches used here clearly have different strengths in application. Targeted surveillance appears to be an effective strategy for detecting new CWD foci. Among the six most intensively monitored MUs in northcentral Colorado (C7, C8, C9, C19, C191, C20), CWD was confirmed in 66% (74/112) of suspect deer and 43% (23/54) of suspect elk submitted via targeted surveillance; by comparison, only 5% (92/1826) of deer and 0.5% (5/929) of elk randomly sampled in these same MUs actually appeared to be infected with CWD. However, targeted surveillance data are not good predictors of CWD prevalence or temporal trends because they are likely biased in several respects (e.g., dependence on public awareness, on someone observing and reporting sick animals, and on interests of local management personnel). This is evident in the poor relationship between the number of clinical cases and estimated prevalence (Fig. 3). Suspect case submission rates appear to have been strongly influenced by the distribution of human population centers within the endemic area (Fig. 2). Similarly, the seasonal pattern of clinical disease could reflect increased observability of deer and elk on winter ranges. Alter-

natively, because clinical cases also tend to occur with greater frequency in captive deer during winter (M. W. Miller, unpubl. data), this pattern may reflect effects of cold temperatures and/or inclement weather in precipitating or exacerbating clinical CWD in infected individuals. Although probably less effective in detecting new disease foci, harvest-based surveys appear to produce relatively unbiased prevalence data (Conner et al., 2000), and therefore should serve as a more reliable basis for assessing long-term temporal and spatial trends in CWD dynamics.

Sex- and age class-specific prevalence data are consistent with previous reports that adult cervids may contract CWD (Williams and Young, 1992; Miller et al., 1998). These data also support the hypothesis that lateral transmission drives CWD dynamics. In light of an estimated 18 to 24 mo or greater incubation period for CWD in deer (Miller et al., 1998; E. S. Williams, unpubl. data), the relative lack of preclinical disease in 16- to 17-mo-old deer argues against maternal transmission being the most common route for CWD transmission. If maternal transmission were common, then infected animals should occur predominantly in younger age classes (e.g., Foster and Dickinson, 1989); this should be more evident among does than bucks, because a broader range of female age classes are represented under current harvest regimes in the core endemic area (Fig. 4). Our epidemic models also supported the apparent importance of lateral transmission in CWD dynamics: prevalence levels observed in field surveys could not be achieved or sustained in modeled deer populations in the absence of lateral transmission, but CWD could be sustained without maternal transmission. A similar relationship between lateral and maternal transmission also emerged in recent epidemic models of scrapie (Matthews et al., 1999; Woolhouse et al., 1999). Although not represented in our models, indirect transmission via environmental contamination (Williams and Young, 1992; Miller et al., 1998; M. W. Miller, unpubl. data; E. S. Williams, unpubl. data) may play a role in natural dynamics and persistence of CWD and deserves further consideration.

Our observations may offer insights into the ultimate origins of CWD. The "chronic wasting disease" syndrome was first recognized by biologists in the 1960s among captive mule deer held in two wildlife research facilities in Fort Collins (Colorado, USA); subsequently it was recognized in captive deer, and later in captive elk, in other wildlife research facilities near Kremmling (Colorado) and Wheatland (Wyoming) (Williams and Young, 1980, 1982). Although CWD was first recognized in captive deer, whether it truly originated in these facilities is less clear. Assuming that prevalence increases slowly over several decades, as forecast by our models, and that such increases are uniform across populations and over time, it follows that CWD prevalence should be highest in areas where it has been present longest (provided its introduction is relatively recent). Applying these assumptions to our field data, the pattern of geographic variation in prevalence observed here suggests an epicenter of highest prevalence well north of Fort Collins, with subsequent spread among deer subpopulations north and south along the Front and Laramie Range foothills and east via the Laramie/North Platte and Cache la Poudre/South Platte river drainages. This hypothesized pattern of disease spread would be consistent with established migration and movement corridors for mule deer, which are particularly well-documented along the Poudre/South Platte river corridor in northeastern Colorado (Siglin, 1965; Kufeld et al., 1989; Kufeld and Bowden, 1995; M. W. Miller, unpubl. data). Because the Fort Collins research facilities where CWD was first described sit near the periphery of the MU aggregates where CWD prevalence is currently highest, the notion (Spraker et al., 1997) that these facilities were the original source of CWD seems questionable. Although infected research

facilities historically may have exacerbated geographic spread of CWD, we detected no infections among 360 deer sampled in five Colorado MUs (18, 28, 37, 181, 371) near Kremmling (Colorado) where CWD-infected captive mule deer also were held in the late 1970s and early 1980s. Alternatively, some combination of unidentified local conditions may enhance CWD transmission in certain areas and prevent its establishment in others, thereby creating the geographic variation in disease prevalence reported here.

The duration of CWD's occurrence in free-ranging cervids remains as enigmatic as its geographic origin. Chronic wasting disease probably has been occurring in captive deer for >30 yr (Williams and Young, 1980, 1982, 1992). Although first documented in the wild in 1981 (Spraker et al., 1997), it is highly unlikely that this was the first case of CWD in a free-ranging cervid. A review of archived CDOW records revealed that a free-ranging mule deer with clinical CWD was probably misdiagnosed in 1978 (M. W. Miller, unpubl. data). Undiagnosed cases could have occurred even earlier. In contrast to clinical submissions, historical data on CWD prevalence are lacking throughout most of the endemic area. However, our experiences with targeted surveillance suggest prevalence may be 1% (or higher) by the time clinical cases are first detected in the field. Assuming prevalence was about 1% in the MU (C19) west of Fort Collins where the first clinical case in a free-ranging mule deer was confirmed in 1984, model projections (Fig. 5D) appear consistent with an increase to about 3.5% over 14 yr. Similarly, model projections approximate the epidemic curve for one Wyoming MU (W64) where the first clinical case in a free-ranging mule deer was confirmed in 1985 and observed prevalence has apparently increased from ≤2.9% to 13% between 1983 and 1998 (E. S. Williams, unpubl. data) (Fig. 5D). The foregoing models produce 0.5 to 0.7% annual increases in prevalence that would be difficult to detect in the short term with our sample sizes. Time scales associated with these epidemic curves suggest the possibility that CWD may have been present in free-ranging deer in portions of both northeastern Colorado and southeastern Wyoming since the early 1960s, if not earlier.

Effective strategies for controlling or eliminating CWD in wild deer and elk have not been identified. Culling only deer and elk with clinical signs leaves preclinical individuals in the population; the relatively small number of clinical cases detected in our highest prevalence areas (Fig. 3) illustrate the poor efficacy of such approaches. Despite aggressive harvest regimes in some portions of the endemic area that reduced survival rates for male deer to less than half that for females, CWD was equally prevalent among males and females. It follows that random culling via harvest or other means may be relatively ineffective in reducing CWD prevalence, although local deer population densities and the unknown magnitude of female-to-male transmission confound such interpretations. Left unmanaged, the significance of CWD and its impacts on populations are uncertain, but models predict that epidemics sustained over 30 to 50 yr could reduce affected mule deer populations dramatically. As modeled, CWD epidemics are self-limiting because they drive affected populations to extinction. A similar epidemic pattern was observed in a sheep flock naturally infected with scrapie (Foster and Dickinson, 1989). Such patterns also have been seen in captive mule deer and white-tailed deer herds with CWD (Williams and Young, 1992; M. W. Miller, unpubl. data); however, epidemic dynamics are more rapid in captive deer and much higher transmission coefficients (e.g., $\beta = 3.5$) are required to simulate CWD epidemics in captive deer populations, suggesting that more intensive transmission may occur under confinement than in the wild. Because population and epidemic dynamics in naturally-infected free-ranging deer populations occupying

large geographic areas are more complex than either modeled or captive deer herds, the ultimate outcome in endemic areas seems less certain.

Based on our findings, CWD appears to be an emerging TSE of local and potentially broader importance. Endemic CWD apparently can be sustained in free-ranging cervid populations for decades. Moreover, our models suggest that endemic CWD may be more properly viewed as an epidemic with a protracted time scale. Chronic wasting disease may have been spreading eastward along the North and South Platte rivers for well over a decade. Natural geographic spread will probably continue, but may be virtually impossible to detect in earliest stages. Such spread may be accelerated in the future by infected white-tailed deer and elk populations: river bottom white-tailed deer are highly mobile (Kufeld and Bowden, 1995) and become increasingly abundant in habitats east of the present endemic area, and elk populations may be more likely than mule deer to sustain CWD in higher elevation winter ranges to the west of the present endemic area. It follows that barriers to the natural spread of CWD and viable population-level strategies for its management clearly warrant further evaluation.

ACKNOWLEDGMENTS

Our work was supported by Federal Aid in Wildlife Restoration Project W-153-R, the Colorado Division of Wildlife, Wyoming Game and Fish Department, University of Wyoming, Colorado State University, and a small grant from USDA Veterinary Services. We thank S. Berry, A. Case, W. Cook, B. Cummings, H. Edwards, S. Hendrix, P. Jaeger, B. Lanka, S. Tracey, V. Welch, L. Wheeler, E. Zimmerman, B. Zink, and many other agency and institutional personnel for field and/or laboratory assistance; K. O'Rourke and R. Rubenstein generously provided antibodies and technical advice for conducting IHCs. D. Freddy, J. Reif, and M. Wild, as well as several anonymous reviewers, provided useful reviews of previous drafts of this manuscript.

LITERATURE CITED

AGRESTI, A. 1990. Categorical data analysis. John Wiley & Sons, Inc. New York, New York, 558pp.

———, AND B. A. COULL. 1998. Approximate is better than "exact" for intervals of binomial proportions. American Statistician 52: 119–126.

ANDERSON, R. M., C. A. DONNELLY, N. M. FERGUSON, M. E. J. WOODHOUSE, C. J. WATT, H. J. UDY, S. MAWHINNEY, S. P. DUNSTAN, T. R. E. SOUTHWOOD, J. W. WILESMITH, J. B. M. RYAN, L. J. HOINVILLE, J. E. HILLERTON, A. R. AUSTIN, AND G. A. H. WELLS. 1996. Transmission dynamics and epidemiology of BSE in British cattle. Nature 382: 779–788.

BARTMANN, R. M., G. C. WHITE, AND L. H. CARPENTER. 1992. Compensatory mortality in a Colorado mule deer population. Wildlife Monographs 121: 1–39.

BEAR, G. D. 1989. Seasonal distribution and population characteristics of elk in Estes Valley, Colorado. Special Report Number 65, Colorado Division of Wildlife, Fort Collins, Colorado, 14 pp.

BRUCE, M. E., R. G. WILL, J. W. IRONSIDE, I. MCCONNELL, D. DRUMMOND, A. SUTTIE, L. MCCARDLE, A. CHREE, J. HOPE, C. BIRKETT, S. COUSENS, H. FRASER, AND C. J. BOSTOCK. 1997. Transmissions to mice indicate that 'new variant' CJD is caused by BSE agent. Nature 389: 498–501.

BURNHAM, K. P., AND D. R. ANDERSON. 1998. Model selection and inference: A practical information-theoretic approach. Springer-Verlag, New York, New York, 353 pp.

CONNER, M. M., C. W. MCCARTY, AND M. W. MILLER. 2000. Detection of bias in harvest-based estimates of chronic wasting disease prevalence in mule deer. Journal of Wildlife Diseases 36: 691–699.

DETWILER, L. A. 1992. Scrapie. Scientific and Technical Review Office of International Epizootics 11: 491–537.

ERICKSON, J. A., AND W. G. SEIGLER. 1969. Efficient sectioning of incisors for estimating ages of mule deer. The Journal of Wildlife Management 33: 384–388.

FOSTER, J. D., AND A. G. DICKINSON. 1989. Age at death from natural scrapie in a flock of Suffolk sheep. Veterinary Record 125: 415–417.

HADLOW, W. J. 1996. Differing neurohistologic images of scrapie, transmissible mink encephalopathy, and chronic wasting disease of mule deer and elk. *In* Bovine spongiform encephalopathy The BSE dilemma. C. J. Gibbs, Jr. (ed.). Springer-Verlag, New York, New York, pp. 122–137.

HEESTERBEEK, J. A. P, AND M. G. ROBERTS. 1995. Mathematical models for microparasites of wildlife. *In* Ecology of infectious diseases in natural populations. B. T. Grenfell and A. P. Dobson (eds.). Cambridge University Press, Cambridge, England, pp. 90–122.

HOINVILLE, L. J. 1996. A review of the epidemiology of scrapie in sheep. Scientific and Technical Re-

view Office of International Epizootics 15: 827–852.

KUFELD, R. C., AND D. C. BOWDEN. 1995. Mule deer and white-tailed deer inhabiting eastern Colorado plains river bottoms. Technical Publication Number 41, Colorado Division of Wildlife, Fort Collins, Colorado, 58 pp.

———, ———, AND D. L. SCHRUPP. 1989. Distribution and movement of female mule deer in the Rocky Mountain foothills. The Journal of Wildlife Management 53: 871–877.

LARSON, J. S., AND R. D. TABER. 1980. Criteria of sex and age. *In* Wildlife management techniques manual. S. D. Schemnitz (ed.). The Wildlife Society, Washington, D. C. pp. 143–202.

MATTHEWS, L., M. E. WOOLHOUSE, AND N. HUNTER. 1999. The basic reproduction number for scrapie. Proceedings of the Royal Society London B 266: 1085–1090.

MCCARTY, C. W. 1999. Contributions to the mathematical theory of epidemic dynamics. Ph.D. Thesis, Colorado State University, Fort Collins, Colorado, 176 pp.

——— AND M. W. MILLER. 1998. A versatile model of disease transmission applied to forecasting bovine tuberculosis dynamics in white-tailed deer populations. Journal of Wildlife Diseases 34: 722–730.

MILLER, J. M., A. L. JENNY, W. D. TAYLOR, R. F. MARSH, R. RUBENSTEIN, AND R. E. RACE. 1993. Immunohistochemical detection of prion protein in sheep with scrapie. Journal of Veterinary Diagnostic Investigation 5: 309–316.

MILLER, M. W., M. A. WILD, AND E. S. WILLIAMS. 1998. Epidemiology of chronic wasting disease in captive Rocky Mountain elk. Journal of Wildlife Diseases 34: 532–538.

O'ROURKE, K. I., T. V. BASZLER, J. M. MILLER, T. R. SPRAKER, I. SADLER-RIGGLEMAN, AND D. P. KNOWLES. 1998. Monoclonal antibody F89/160.1.5 defines a conserved epitope on the ruminant prion protein. Journal of Clinical Microbiology 36: 1750–1755.

ROBINETTE, W. L., D. A. JONES, G. ROGERS, AND J. S. GASHWILER. 1957. Notes on tooth development and wear for Rocky Mountain mule deer. The Journal of Wildlife Management 21: 134–153.

RUBENSTEIN, R., R. J. KASCSAK, P. A. MERZ, M. C. PAPINI, R. I. CARP, N. K. ROBAKIS, AND H. M. WISNIEWSKI. 1986. Detection of scrapie-associated fibril (SAF) proteins using anti-SAF antibodies in non-purified tissue preparations. Journal of General Virology 67: 671–681.

SAKAMOTO, Y. 1991. Categorical data analysis by AIC. KTK Scientific Publishers, Tokyo, Japan, 314 pp.

SIGLIN, R. J. 1965. Seasonal movements of mule deer in the Cache la Poudre drainage. M.S. Thesis, Colorado State University, Fort Collins, Colorado, 73 pp.

SIGURDSON, C. J., E. S. WILLIAMS, M. W. MILLER, T. R. SPRAKER, K. I. O'ROURKE, AND E. A. HOOVER. 1999. Oral transmission and early lymphoid tropism of chronic wasting disease PrP^{res} in mule deer fawns. Journal of General Virology 80: 2757–2764.

SPRAKER, T. R., M. W. MILLER, E. S. WILLIAMS, D. M. GETZY, W. J. ADRIAN, G. G. SCHOONVELD, R. A. SPOWART, K. I. O'ROURKE, J. M. MILLER, AND P. A. MERZ. 1997. Spongiform encephalopathy in free-ranging mule deer (*Odocoileus hemionus*), white-tailed deer (*O. virginianus*), and Rocky Mountain elk (*Cervus elaphus nelsoni*) in northcentral Colorado. Journal of Wildlife Diseases 33: 1–6.

UNSWORTH, J. W., D. F. PAC, G. C. WHITE, AND R. M. BARTMANN. 1999. Mule deer survival in Colorado, Idaho, and Montana. The Journal of Wildlife Management 63: 315–326.

VAN KEULEN, L. J. M., B. E. C. SCHREUDER, R. H. MELOEN, M. POELEN-VAN DEN BERG, G. MOOIJ-HARKES, M. E. W. VROMÀNS, AND J. P. M. LANGERVELD. 1995. Immunohistochemical detection and localization of prion protein in brain tissue of sheep with natural scrapie. Veterinary Pathology 32: 299–308.

WILLIAMS, E. S., AND S. YOUNG. 1980. Chronic wasting disease of captive mule deer: A spongiform encephalopathy. Journal of Wildlife Diseases 16: 89–98.

———, AND ———. 1982. Spongiform encephalopathy of Rocky Mountain elk. Journal of Wildlife Diseases 18: 463–471.

———, AND ———. 1992. Spongiform encephalopathies of Cervidae. Scientific and Technical Review Office of International Epizootics 11: 551–567.

———, AND ———. 1993. Neuropathology of chronic wasting disease of mule deer (*Odocoileus hemionus*) and elk (*Cervus elaphus nelsoni*). Veterinary Pathology 30: 36–45.

WINELAND, N. E., L. A. DETWILER, AND M. D. SALMAN. 1998. Epidemiologic analysis of reported scrapie in the United States: 1,117 cases (1947–1992). Journal of the American Veterinary Medical Association 212: 713–718.

WOOLHOUSE, M. E. J., L. MATTHEWS, P. COEN, S. M. STRINGER, J. D. FOSTER, AND N. HUNTER. 1999. Population dynamics of scrapie in a sheep flock. Philosophical Transactions of the Royal Society London B 354: 751–756.

Received for publication 17 September 1999.