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A META-BACI APPROACH FOR EVALUATING MANAGEMENT INTERVENTION ON CHRONIC WASTING DISEASE IN MULE DEER

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Abstract. Advances in acquiring and analyzing the spatial attributes of data have greatly enhanced the potential utility of wildlife disease surveillance data for addressing problems of ecological or economic importance. We present an approach for using wildlife disease surveillance data to identify areas for (or of) intervention, to spatially delineate paired treatment and control areas, and then to analyze these nonrandomly selected sites in a meta-analysis framework via before–after–control–impact (BACI) estimates of effect size. We apply these methods to evaluate the effectiveness of attempts to reduce chronic wasting disease (CWD) prevalence through intensive localized culling of mule deer (*Odocoileus hemionus*) in north-central Colorado, USA. Areas where surveillance data revealed high prevalence or case clusters were targeted by state wildlife management agency personnel for focal scale (on average <17 km^2) culling, primarily via agency sharpshooters. Each area of sustained culling that we could also identify as unique by cluster analysis was considered a potential treatment area. Treatment areas, along with spatially paired control areas that we constructed post hoc in a case-control design (collectively called "management evaluation sites"), were then delineated using home range estimators. Using meta-BACI analysis of CWD prevalence data for all management evaluation sites, the mean effect size (change of prevalence on treatment areas minus change in prevalence on their paired control areas) was 0.03 (SE = 0.03); mean effect size on treatment areas was not greater than on paired control areas. Excluding cull samples from prevalence estimates or allowing for an equal or greater two-year lag in system responses to management did not change this outcome. We concluded that management benefits were not evident, although whether this represented true ineffectiveness or was a result of lack of data or insufficient duration of treatment could not be discerned. Based on our observations, we offer recommendations for designing a management experiment with 80% power to detect a 0.10 drop in prevalence over a 6–12-year period.

Key words: BACI; case-control design; chronic wasting disease (CWD); management intervention; meta-analysis; mule deer; Odocoileus hemionus; *prion; transmissible spongiform encephalopathy.*

Introduction

Wildlife ecologists and managers have become increasingly concerned with emerging infectious diseases and the threats they pose to wildlife and human health. Advances in acquiring and analyzing the spatial attributes of wildlife disease surveillance data have greatly enhanced the potential utility of these data for addressing problems of ecological or economic importance. In addition to providing descriptive statistics about epidemics, georeferenced data can also be used to understand spatial heterogeneity and patterns of disease spread, as well as to identify "hot spots" or to target high-risk areas for intervention efforts. West Nile virus (Brownstein et al. 2004), raccoon (*Procyon lotor*) and fox (*Vulpes vulpes*) rabies (Curtis 1999, Jones et al. 2003), and tuberculosis in deer (*Odocoileus* spp.; Miller et al. 2003) are examples of wildlife diseases where availability of spatially explicit surveillance has aided in suggesting target intervention locations and/or strategies. Spatially explicit surveillance data can also be used to evaluate the effectiveness of an intervention where sufficient data and controls are available. It follows that analytical approaches for identifying areas for, or of, intervention treatment, defining treatment and control areas, and comparing trends at these sites would further extend the utility of spatially explicit surveillance data in understanding and controlling epidemics in natural populations.

We developed and applied such approaches to evaluate the effectiveness of management attempts to reduce chronic wasting disease (CWD) prevalence among free-ranging mule deer (*Odocoileus hemionus*) in north-central Colorado. Chronic wasting disease (Williams and Young 1980), a contagious prion disease of deer, wapiti (*Cervus elaphus nelsoni*), and moose (*Alces*

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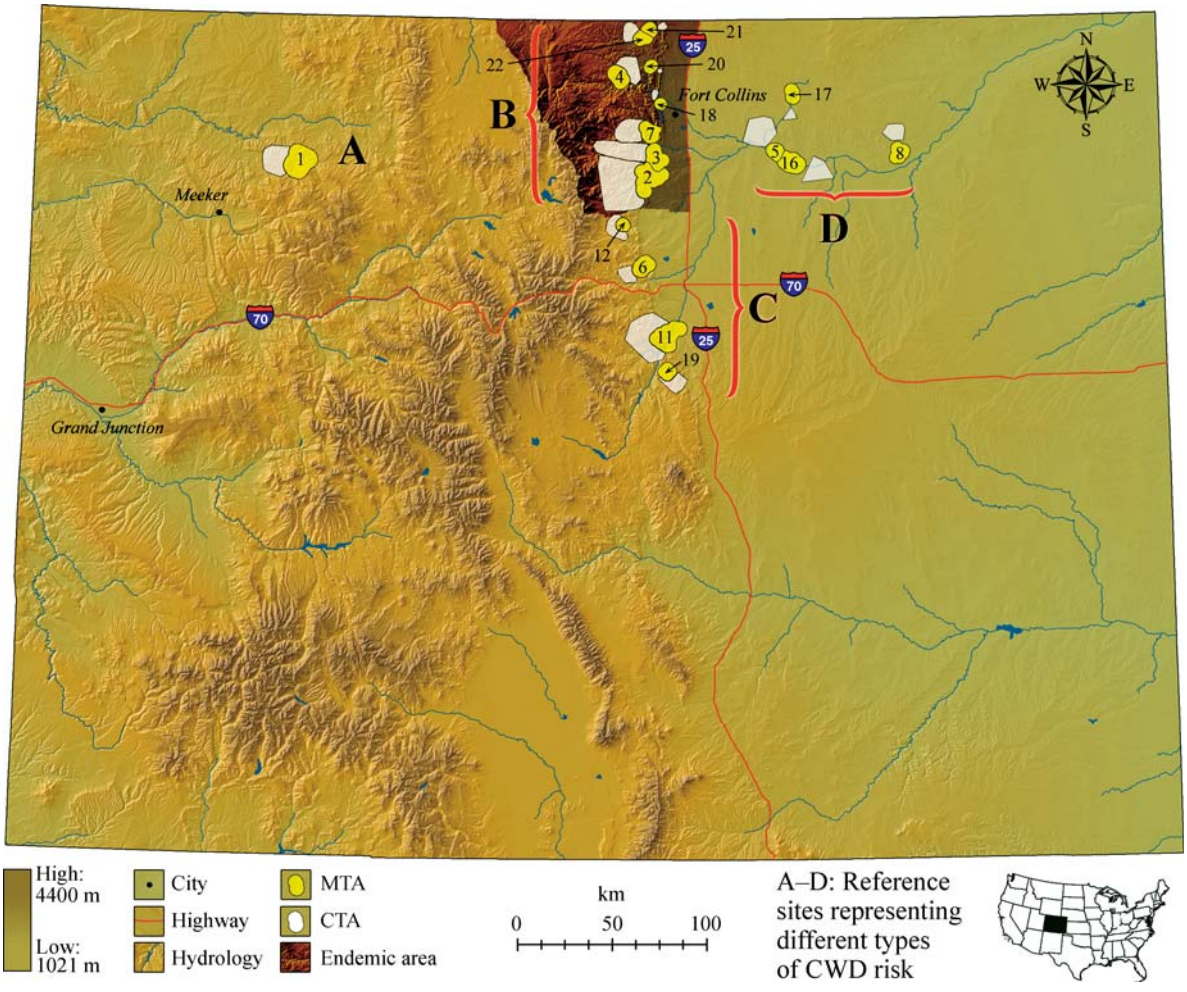

FIG. 1. Locations of management evaluation sites. Each site consisted of a management treatment area (MTA), where mule deer were culled, and its spatially paired control area (CTA). Also noted are (A) the focus area west of the Continental Divide, (B) endemic high-prevalence area, (C) new foci along the Front Range, and (D) areas of CWD infection along the South Platte River.

alces), has emerged as an important wildlife health problem in several parts of North America (Williams and Miller 2002, Williams et al. 2002, Williams 2005). In Colorado, mule deer are the predominant host species (Miller et al. 2000). Both spatial and demographic factors influence observed patterns of CWD prevalence in mule deer: prevalence varies at coarse (Miller et al. 2000) and fine (Conner and Miller 2004, Farnsworth et al. 2005, 2006) geographic scales, and is higher in male middle-aged mule deer than in younger or older age classes or than in females of any age (Miller et al. 2000, Miller and Conner 2005). Whether such factors can be exploited to effect disease control remains unclear.

The Colorado Division of Wildlife (CDOW) has monitored CWD prevalence in north-central Colorado for nearly a decade (Miller et al. 2000, Miller and Conner 2005). Based on initial analyses of prevalence trends and the subsequent detection of a new focus of CWD west of the Continental Divide in early 2002 (Fig. 1, reference site A), wildlife managers in Colorado began efforts to reduce and control CWD prevalence in the winter of 2001–2002 with goals of eliminating CWD from new foci, reducing CWD prevalence in areas of high prevalence, and reducing the risk of CWD spread along putative movement corridors (*public communications*, Colorado Division of Wildlife 2002; Colorado Wildlife Commission Policy, *available online*).[5] A variety of management approaches were employed, including relatively intensive focal culling of deer, primarily via agency sharpshooters, in areas where surveillance data revealed high prevalence or case clusters. The underlying idea was that targeting specific subpopulations of highly infected deer would have wider impacts on exposure risk.

Here, we present an approach for identifying areas of intervention treatment, spatially delineating treatment

[5] ⟨http://wildlife.state.co.us/NR/rdonlyres/63CF1520-378C-45D7-B5A6-3208926D0D1A/0/cwdpolicyreview112.pdf⟩

PLATE 1. Mule deer (*Odocoileus hemionus*) in Estes Valley (control area for evaluation site 3), Colorado, USA. Vegetation and topography are typical for higher elevation sites on the eastern side of the Continental Divide. Photo credit: Victoria Dreitz.

and paired control areas in a case-control design, and analyzing these nonrandomly selected sites in a meta-analysis framework using before–after–control–impact (BACI) estimates of effect size. Our overall objective was to develop methods to allow us to evaluate whether the focal deer culling by CDOW reduced CWD prevalence on a variety of disparate treated areas.

METHODS

Because CWD prevalence is spatially heterogeneous at a relatively fine scale (Conner and Miller 2004, Farnsworth et al. 2006) and mule deer winter ranges in north-central Colorado are relatively small (<10 km^2; Kufeld et al. 1989; M. W. Miller, *unpublished data*), and because culling tended to be localized (core areas typically ≤ 17 km^2), we decided to analyze management effects in the immediate vicinity of culling activities rather than on a larger scale like a game management unit, county, or state. Areas where surveillance data revealed relatively high CWD prevalence or case clusters were subjectively identified and targeted by state wildlife management agency personnel for focal culling during 2001–2004. Each culled area that we could also identify as unique by cluster analysis was considered a potential treatment area, and for these we used spatial home range estimators to delimit the treatment area and its spatially paired control area that we constructed post hoc in a case-control design. We call each treatment area and its paired control area a "management evaluation site." Because our treatments were not randomly assigned, we used a BACI analysis (Green 1979, Stewart-Oaten et al. 1986, Underwood 1994) to estimate the change in prevalence on treatment areas relative to their control areas (effect size) for each site, and then tested whether the effect was significant using a meta-analysis framework (Wolf 1986, Gurevitch et al. 1992). Our goal was simply to estimate the effects of focal animal culling; we did not attempt to test hypotheses about underlying mechanisms of potential effects on transmission mechanisms like density dependence per se because we had no estimates of deer density on management evaluation sites. Based on what we learned from this analysis, we formulated several monitoring strategies to adaptively refine and improve future management experiments (Marcot 1998) to detect two relevant effect sizes with high power.

Study area

Colorado Division of Wildlife conducted disease management culls in northwestern Colorado (Fig. 1, reference A), along the eastern front of the Rocky Mountains (Fig. 1, references B and C; see Plate 1), and along the South Platte River corridor (Fig. 1, reference D). The study site in northwestern Colorado was centered around lower elevations of the Williams Fork of the Yampa River, where there was relatively low annual precipitation and vegetation types were in the Great Basin zone with sage grasslands and shrubland patches. Vegetation in sage grasslands included big sagebrush (*Artemisia tridentata*), bitterbrush (*Purshia tridentata*), rabbitbrush (*Chrysothamnus nauseosus*), and mixed grasses. Shrubland patches included Gambel's oak (*Quercus gambelii*), serviceberry (*Amelanchier alnifolia*), mountain mahogany (*Cercocarpus montanus*), chokecherry (*Prunus virginiana*), and snowberry (*Symphoricarpos utahensis*). Management evaluation sites along the eastern edge of the Rocky Mountains were primarily in lower elevation areas (<2000 m) where mule deer wintered, and consisted of rolling foothills,

high prairie, and rural/urban areas. Vegetation in non-urban area was primarily sagebrush-steppe habitat with big sagebrush, antelope bitterbrush, mountain mahogany, and mixed grasses. Urbanized areas were interspersed with rural areas with numerous small ranches and agricultural fields. The eastern plains management evaluation sites were at $<$1500 m and included riparian bottom lands of the South Platte River and prairie. Riparian vegetation was cottonwood–willow (*Populas sargentii–Salix* spp.) or saltcedar tamarisk (*Tamarix pentandra*). Prairie areas were vegetated by short and mid-grasses such as buffalograss (*Buchloe dactyloides*) and bluegrama (*Bouteloua gracilis*), and other grasses, along with sand sagebrush (*Artemisia filifolia*) in rolling sandhills and unfarmed uplands. For all non-urbanized areas, land use was primarily a mix of cattle ranching and dry-crop farming, with some irrigated farming near the South Platte River, and there was a mix of public and private lands.

Management intervention

The specific management intervention evaluated here was lethal removal of adult mule deer in the immediate vicinity of subjectively defined clusters of CWD cases in deer, hereafter referred to collectively as "focal culling" or "culling." Deer were killed either by agency sharpshooters or public hunters working in defined areas at most sites; in a few areas where shooting was not feasible, deer were darted with anesthetic drugs and euthanized or were captured in Clover traps or under drop nets and euthanized. Most culling occurred during January–April of each year, beginning in 2001. Carcasses of all culled deer were sampled and tested for CWD infection. In all, some level of culling ($\geq$10 deer removed) was undertaken at 22 different locations; of these, only 16 sites had sufficient data before and after treatment to be analyzed (Table 1).

Data samples

Sampled mule deer were classified as CWD positive (=infected) or negative (=uninfected) based on immunohistochemical exam of retropharyngeal lymph node or tonsil tissue (Miller and Williams 2002); CWD surveillance and diagnostic methods were as described elsewhere (Miller et al. 2000, Miller and Williams 2002, Hibler et al. 2003). There were two data sets; one was used to delineate treatment and control areas, and the other was use to estimate prevalence on the treatment and control areas. The data set used to delineate treatment and control areas included mule deer taken during disease management culling and hunting as part of CWD management efforts during December 2001–June 2005 (M. W. Miller, *unpublished data*). We call these samples "management samples." The data set used to estimate prevalence on the treatment and control areas (after they were delineated) included mule deer harvested by hunters during September 1996–June 2005 (Miller et al. 2000, Miller and Conner 2005; M. W. Miller, *unpublished data*), apparently healthy mule deer killed by wildlife managers during December 2001–June 2005 (Miller and Conner 2005; M. W. Miller, *unpublished data*), and mule deer taken during disease management culling and hunting as part of CWD management efforts during the period from December 2001 to June 2005 (M. W. Miller, *unpublished data*). We call these samples "surveillance samples."

All georeferenced surveillance samples were used to estimate CWD prevalence in subsequent data analysis with two restrictions. First, we restricted data to only males because few females were sampled before management intervention. Second, because CWD is rare in mule deer less than one year old (Miller et al. 2000) we only used data from male mule deer $\geq$1.3 years old. Because we knew that prevalence varied between young (2–4 years) and older males (5–7 years; Miller and Conner 2005), we further evaluated the age-structure of the samples. Thus, only surveillance samples of adult male mule deer were used in our analyses.

Site selection and delineation

We defined a management evaluation site as a pair of spatially explicit polygons: a management treatment area (MTA) where steady culling took place, and a spatially paired reference site, or control treatment area (CTA). Locating individual MTAs involved the use of clustering methods to place management samples into spatially disjunct groups. Exploratory data analysis suggested the need for a clustering method that could detect an unknown number of clusters of unequal size and dispersion and with irregular shapes. To meet these restrictions, we used a density-based clustering algorithm (Scott 1992, Zaiane et al. 2002) using PROC MODECLUS in SAS, Version 8.02 (SAS 1999). We selected a value of 3 km for the smoothing parameter (i.e., kernel support sphere and clustering neighborhood radius) based on information from a previous mule deer study (Conner and Miller 2004). The results from this analysis allowed us to assign management samples to potential MTA groups such that samples within groups were spatially similar, and samples in different groups were spatially dissimilar.

To delineate the MTA polygons we first identified "core" areas from a kernel density estimate using ArcView GIS 3.2 (ESRI, Redlands, California, USA) with the animal movements extension (Hooge and Eichenlaub 2000). This step (equivalent to home range estimation) used least squares cross validation to estimate the smoothing parameter (Worton 1989). We chose a 95% utilization distribution to represent the core of a management treatment area (Fig. 2A). To account for movement of animals using the core area and to better represent the zone we expected management actions to influence, we buffered these core areas based on previous movement analysis. Once mule deer reached winter ranges (where most samples were collected), from previous analyses we estimated that 85% of all distances

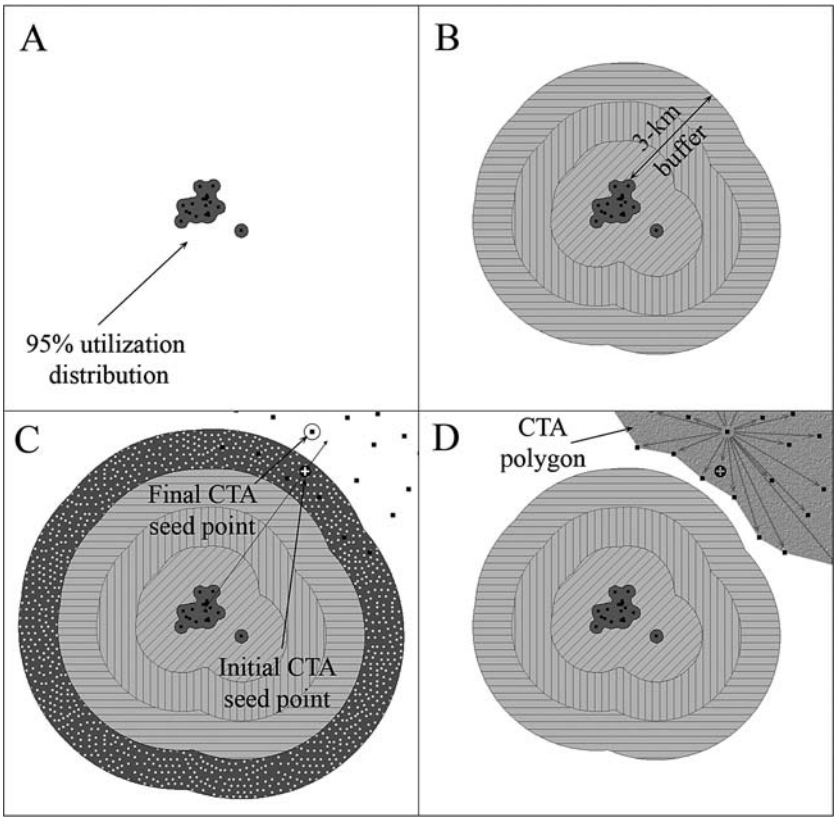

FIG. 2. A graphical example of the sequential steps used to construct a management evaluation site by delimiting management treatment area (MTA) and control treatment area (CTA) polygons. (A) The 95% utilization distribution of management samples defining the MTA core area. (B) The 3-km buffer of the core area representing the extent of the MTA polygon. (C) A random seed selected from a 1-km buffer of the MTA. The nearest surveillance sample 1 km beyond the initial seed is selected as the final CTA seed. (D) The final CTA polygon containing the same number of surveillance samples as the MTA. Arrows represent nearest neighbors (from the final seed) that were included to build the polygon.

moved were <3 km (Conner and Miller 2004). Thus, MTA polygons represented a core area that was the focus of management intervention, and a 3 km buffer to account for movements of animals using the core area (Fig. 2B). Although initial MTA construction included all cluster groups, we considered polygons based on fewer than 10 management samples too few removals to qualify as a management treatment group. These small groups were removed from the list of potential management treatment areas. To reduce bias in control groups, any surveillance samples contained by these small polygons were also unavailable for membership in a control group.

Following the specific recommendation of Stewart-Oaten et al. (1986), we attempted to choose control areas sufficiently far from culling activity to be largely free from direct influence, yet close enough to be influenced by the same range of environmental phenomena. Because MTAs include a buffer surrounding the core treatment area, we considered any sample outside the total treatment area independent from the treatment samples. Selection of CTA polygons involved an iterative process of adding the next nearest neighbor to a "seed point." This resulted in an expansion of the control area until the number of surveillance samples equaled that of its matching MTA (Fig. 2C). Initially, control seeds were selected randomly from the set of all surveillance samples within 1 km of the MTA perimeter. Because the CTA is dependent on the MTA this resulted in many control areas haloing their MTA polygons. To avoid this "halo effect" and make CTAs more similar to MTAs, a new point was selected 1 km from the randomly selected point along a line connecting the original seed with the center of the MTA polygon (Fig. 2D). The nearest surveillance sample to this point was considered the seed of a control polygon. Taking the minimum convex polygon of the surveillance samples created the final CTA polygon (Fig. 2D).

BACI analysis

Prevalence on MTAs and CTAs was estimated as the number of CWD-positive surveillance samples divided by the total number of surveillance samples located within the delineated CTAs and MTAs by year and for the entire periods before and after management intervention began. We used 15 June, which we consider the

start of a mule deer biological year (peak parturition; Miller and Conner 2005), as the breakpoint for before and after periods of intervention. Because culling occurred during January–April, the "before" period included surveillance samples collected before the breakpoint plus samples from the first season of culling from a site, while the "after" period included all samples collected in biological years after the first culling season; this seemed logical because cases encountered in the first season's removals were a product of processes that occurred before management intervention. Furthermore, because hunting seasons (the source of >95% of all surveillance samples) occurred during September–December, there was, for analysis purposes, a de facto ~0.7-year lag incorporated after the start of intervention before data were first collected for the "after" period.

Because prevalence of older males (5–7 years) is 2.5 times higher than in younger males (2–4 years) and 7.8 times higher than in yearlings (Miller and Conner 2005), differences in age structure between MTAs and CTAs could confound results. Each year, all CWD-positive harvested and culled deer and a subset of randomly selected CWD-negative deer were aged via cementum annuli examination (Erickson and Seigler 1969, Larson and Taber 1980). A total of 26% ($n = 739$ deer) of the surveillance samples were of known age, either because they were yearlings or because they were tooth aged. From this subsample, we tested for differences in age structure between MTAs and CTAs during the before and after periods using a chi-square test. We grouped the data into older, younger, and yearling male age categories to meet the cell-size requirements of the chi-squared test, and because prevalence in male mule deer varies between these classes (Miller and Conner 2005).

From an initial assessment of available surveillance data, we found that we lacked sample sizes to reliably estimate local prevalence annually because most (67%) of the annual sample sizes were ≤10 deer per MTA. Thus, we pooled all samples into one "before" and one "after" period for each potential MTA and CTA in subsequent analyses. We defined our effect size as the change in prevalence (before minus after) on a MTA minus the change on its CTA expressed as

$$\hat{d}_i = (\hat{p}_{\text{mb}} - \hat{p}_{\text{ma}}) - (\hat{p}_{\text{cb}} - \hat{p}_{\text{ca}})$$

and

$$\text{SE}(\hat{d}_i) = \sqrt{\text{var}(\hat{p}_{\text{mb}}) + \text{var}(\hat{p}_{\text{ma}}) + \text{var}(\hat{p}_{\text{cb}}) + \text{var}(\hat{p}_{\text{ca}})}$$

where $\hat{d}_i$ = relative drop on site i, $\hat{p}$ = estimated prevalence with the following subscripts: mb, MTA before intervention; ma, MTA after intervention; cb, CTA before intervention; and ca, CTA after intervention.

Positive values for "relative drop" (= effect) indicate that culling reduced prevalence on a treatment area relative to its control. We call this a "relative drop" because it may not represent a true decrease of prevalence; that is, if CWD prevalence on a treatment area increased relatively less than on its paired control site, then this would still be considered a successful management intervention reflected by a positive effect size.

Meta-analysis

Meta-analysis allows synthesis of data from different studies (Gurevitch et al. 1992) or independent areas where areas (in this case management evaluation sites) were considered the sampling units (Wolf 1986). For our meta-analysis, we estimated the weighted mean relative drop and its standard error. We used the reciprocal of the variance of relative drop to weight estimates from each site (Burnham et al. 1987). To test whether differences on all management evaluation sites collectively showed an effect of management culling, we performed a nonparametric Wilcoxon paired-sample test (Zar 1984) and paired t test for the null and alternative hypotheses:

H_0: Mean change in prevalence on MTAs (before − after management intervention) ≤ mean change in prevalence on paired CTAs (before − after management intervention).

H_A: Mean change in prevalence on MTAs (before − after management intervention) > mean change in prevalence on paired CTAs (before − after management intervention).

The null hypothesis could also be stated as: mean relative drop ≤ 0.

To further explore possible explanations for the results of our initial analyses, we also reran the foregoing analyses after excluding data from surveillance samples to allow for a lag of at least two years in CWD system responses to management intervention. That is, we only used "after" samples taken two or more years after management intervention began.

To evaluate if there was a relationship between changes in prevalence on CTAs and their paired MTAs, we regressed the change in CWD prevalence on MTAs (after – before) against the change on CTAs (after – before). We weighted each pair by the reciprocal of the variance of the effect size to account for differences in sample sizes and sampling variance on each area. We used after – before for our regression because the slope of the line is more readily interpretable than before – after.

Post hoc study design

From a review of environmental field studies aimed at detecting an intervention effect, Eberhardt and Thomas (1991) concluded "that the major [problem] is the inadequate sample sizes used in contemporary field experimentation." We did not want to succumb to this

TABLE 1. A summary of 16 spatially paired management treatment areas (MTA) and control treatment areas (CTA) receiving management intervention for chronic wasting disease (CWD), and their associated management samples taken on the MTAs in Colorado, USA, from 2001 to 2005.

Site ID	MTA size (km^2)	CTA size (km^2)	CWD prevalence†	Adult males (N)	Immature males (N)	Adult females (N)	Immature females (N)	Total removed (N)	Management start date	Management end date
2	217	559	0.158	79	13	145	23	260	2002	2005
3	128	240	0.159	32	7	66	8	113	2002	2005
4	110	115	0.064	29	3	74	4	110	2002	2004
5	70	221	0.038	21	7	45	6	79	2001	2004
6	107	66	0.000	2	1	32	2	37	2003	2004
7	103	157	0.185	15	2	35	2	54	2002	2005
8	98	86	0.121	11	1	20	1	33	2001	2003
11	214	343	0.026	4	4	25	5	38	2003	2005
12	46	85	0.000	1	3	15	2	21	2002	2002
16	132	137	0.000	2	0	11	2	15	2002	2004
17	75	28	0.000	4	2	7	1	14	2002	2002
18	36	18	0.071	1	4	7	2	14	2002	2002
19	73	81	0.000	0	1	12	1	14	2003	2004
20	45	7	0.333	4	0	5	0	10	2003	2005
21	50	20	0.000	3	1	6	0	10	2002	2004
22	63	70	0.000	3	2	4	2	11	2004	2005

Note: See Fig. 1 for locations of management evaluation sites.
† Prevalence of CWD in management samples (only culled deer).

malady in future work. We wanted to use the data and model developed for this analysis to improve the monitoring design in order to assure detection of an effect of culling (or other management method) when it occurs; thus we conducted prospective power simulations for the meta-analysis design. We ran Monte Carlo simulations to determine the minimum number of samples required to detect a 5% or 10% relative drop on a MTA with $\geq$80% power for realistic initial prevalences, with the same null and alternative hypotheses as described for the meta-analysis. Samples were bootstrapped from a binomial distribution. We ran 1000 Monte Carlo trials with the following input and outputs.

Inputs.—(1) Number of years: 6–12, equally divided into periods before and after intervention (i.e., 6 years represents 3 before years and 3 after years); (2) number of experimental sites: 3–10; (3) number of samples collected per year: 10–50 incremented by 5 (i.e., 10 samples/yr represents 10 for a MTA and 10 for a CTA, for a total of 20 samples/yr); (4) prevalence on MTAs: 0.15 and 0.10 before and 0.05 after intervention; (5) prevalence on CTAs: 0.10 before and 0.10 after intervention.

Power outputs ($\alpha = 0.10$ for all tests).—(1) Proportion of times each single site had a significant Z score; (2) proportion of times a one-sided paired t test was significant; (3) proportion of times a Wilcoxon paired-sample S statistic was significant. We used a one-sided Wald statistic and $\alpha = 0.10$ to determine significance. Power was estimated as the number of times a case was significant divided by the number of simulations. The outputs allowed us to compare the parametric and nonparametric tests for a meta-analysis approach to a single-site approach. We note that our power to detect a drop in prevalence was higher than if our initial prevalence was around 0.5 due to theoretical variance of a binomial distribution; however the observed prevalences in the areas of concern were typically in the range of 0.10–0.15 (see Input 4).

RESULTS

Of the 22 management evaluation sites having the minimum number of management samples to be included in analyses, 16 (all but management evaluation site 1, which was included for reference; Fig. 1) had surveillance data both before and after management intervention on MTAs and CTAs and were used in subsequent analyses. Culling intensity, prevalence, and area size varied widely between management evaluation sites (Table 1). The total number of deer culled averaged 52 (median = 27), prevalence in management samples averaged 0.07 (median = 0.03), and size (core area plus 3-km buffer) averaged 98 km^2 (median = 87) on MTAs and 139 km^2 (median = 85 km^2) on CTAs. For deer of known age, the age structure of surveillance samples was independent of being from a MTA or CTA during the before ($\chi^2 = 4.171$, df = 2, $P = 0.124$) and after ($\chi^2 = 3.605$, df = 2, $P = 0.165$) periods when ages were grouped as yearlings, younger (2–4 years), and older (5–7 years).

Of the 16 sites with sufficient data, seven showed some evidence of management effect in that the effect on the treatment area was relatively larger than its paired control area, and two of these areas had significant results (for $\alpha = 0.10$, Table 2). The mean effect size was 0.03 (SE = 0.03). However, we failed to reject our null hypothesis: the effect size on MTAs was not greater than on their paired CTAs ($S = 11$, $n = 16$, $P = 0.281$, one-sided). A more powerful parametric one-sided t test yielded similar results ($t = 0.837$, df = 14, $P = 0.208$).

Excluding samples from prevalence estimates to allow for a lag of two or more years in system responses to management did not change this outcome. For the

TABLE 2. Estimated chronic wasting disease (CWD) prevalence for adult male mule deer and effect size for 16 spatially paired management treatment areas (MTA) and control treatment areas (CTA) receiving disease management in the form of focal culling and/or harvest in Colorado, USA.

Site ID	Period†	CTA (N)	MTA (N)	CTA prevalence	MTA prevalence	CTA (before − after)	MTA (before − after)	Effect size: MTA − CTA (±SE)	Wald statistic (Z)	Probability ($>Z$)
2	B	102	144	0.020	0.104					
2	A	209	164	0.067	0.201	−0.047	−0.097	−0.050 (0.046)	−1.080	0.860
3	B	46	36	0.109	0.083					
3	A	73	83	0.205	0.253	−0.097	−0.170	−0.073 (0.094)	−0.770	0.780
4	B	111	89	0.099	0.090					
4	A	93	114	0.151	0.079	−0.051	0.011	0.062 (0.061)	1.020	0.150
5	B	15	9	0.067	0.111					
5	A	17	23	0	0.087	0.067	0.024	−0.043 (0.143)	−0.300	0.620
6	B	42	47	0	0.106					
6	A	13	8	0	0.125	0.000	−0.019	−0.019 (0.133)	−0.140	0.560
7	B	72	90	0.028	0.167					
7	A	83	65	0.012	0.169	0.016	−0.003	−0.018 (0.065)	−0.280	0.610
8	B	4	8	0	0.125					
8	A	17	13	0.176	0.231	−0.176	−0.106	0.071 (0.199)	0.360	0.360
11	B	32	36	0.031	0.139					
11	A	17	13	0	0	0.031	0.139	0.108 (0.066)	1.620	0.050
12	B	9	10	0	0					
12	A	51	50	0.020	0	−0.020	0.000	0.020 (0.020)	1.000	0.160
16	B	5	6	0	0					
16	A	9	8	0.333	0.125	−0.333	−0.125	0.208 (0.208)	1.000	0.160
17	B	5	6	0	0.333					
17	A	4	3	0	0	0.000	0.333	0.333 (0.211)	1.580	0.060
18	B	22	27	0.091	0.111					
18	A	17	12	0.118	0.333	−0.027	−0.222	−0.195 (0.186)	−1.050	0.850
19	B	11	10	0	0					
19	A	6	7	0	0	0.000	0.000	0.000		
20	B	17	12	0.176	0.25					
20	A	7	12	0	0.083	0.176	0.167	−0.010 (0.182)	−0.050	0.520
21	B	30	28	0.3	0.179					
21	A	2	4	0.5	0.25	−0.200	−0.071	0.129 (0.570)	0.230	0.410
22	B	58	63	0.207	0.206					
22	A	10	5	0.1	0.2	0.107	0.006	−0.101 (0.236)	−0.430	0.670

Note: Estimates are based on georeferenced surveillance samples collected from September 1996 to June 2005.
† B, before management intervention began; A, after management intervention.

lagged data, eight sites had sufficient data for the analysis; four of those showed some evidence of management effect in that the effect on the treatment area was relatively larger than its paired control area, but the results were not significant for any site ($P \geq 0.16$). The mean effect size was 0.01 (SE = 0.05). We failed to reject our null hypothesis: the effect size on MTAs was not greater than on their paired CTAs ($S = 3$, $n = 8$, $P = 0.344$, one-sided). A more powerful parametric one-sided t test yielded similar results ($t = 0.316$, df = 14, $P = 0.381$).

When we regressed change in prevalence on MTAs (after − before) against the change on CTAs, a quadratic model (Fig. 3A) fit the data better than a linear model ($\Delta AIC_c = 2.8$). Analysis of residuals indicated no violation of assumptions. Predicted values were generally in the effect region (Fig. 3B), but the upper 95% confidence limits for this curve included predicted values outside of the effect region (Fig. 3A).

Simulations revealed that analyzing the data in a meta-analysis framework was more powerful than when each site was considered separately for all combinations of number of years, samples, and experimental sites. This pattern held for the most efficient designs (i.e., lowest sample sizes): 40 samples/yr were required to achieve 80% power for a single site design (Fig. 4A), but the meta-analysis designs required 10–12 samples/yr (Fig. 4B, C). For parametric and nonparametric meta-analyses, as well as single site analyses, the strategies that achieved ≥80% power with the lowest number of samples were five experimental sites with data collected for eight years (i.e., four before and four after) and six experimental sites with data collected for six years (Fig. 4). Power for the nonparametric Wilcoxon paired-sample test (Fig. 4C) was only slightly less powerful than the paired t test (Fig. 4B). Because it is difficult to assess whether the normality assumption is met for such a small number of experimental sites (four or six), we used the results from the Wilcoxon paired-sample test for all subsequent results and discussion.

Note that simulation results are for a biologically relevant age and sex class. That is, when we recommend 12 samples/yr we mean, for example, 12 adult males, or 12 young males, or 12 females, since prevalence varies widely between these classes. For our given input parameters, a meta-analysis, 80% power, and a 10% net effect size (i.e., a change from 15% to 5% in prevalence in MTAs with no change in CTAs), 120

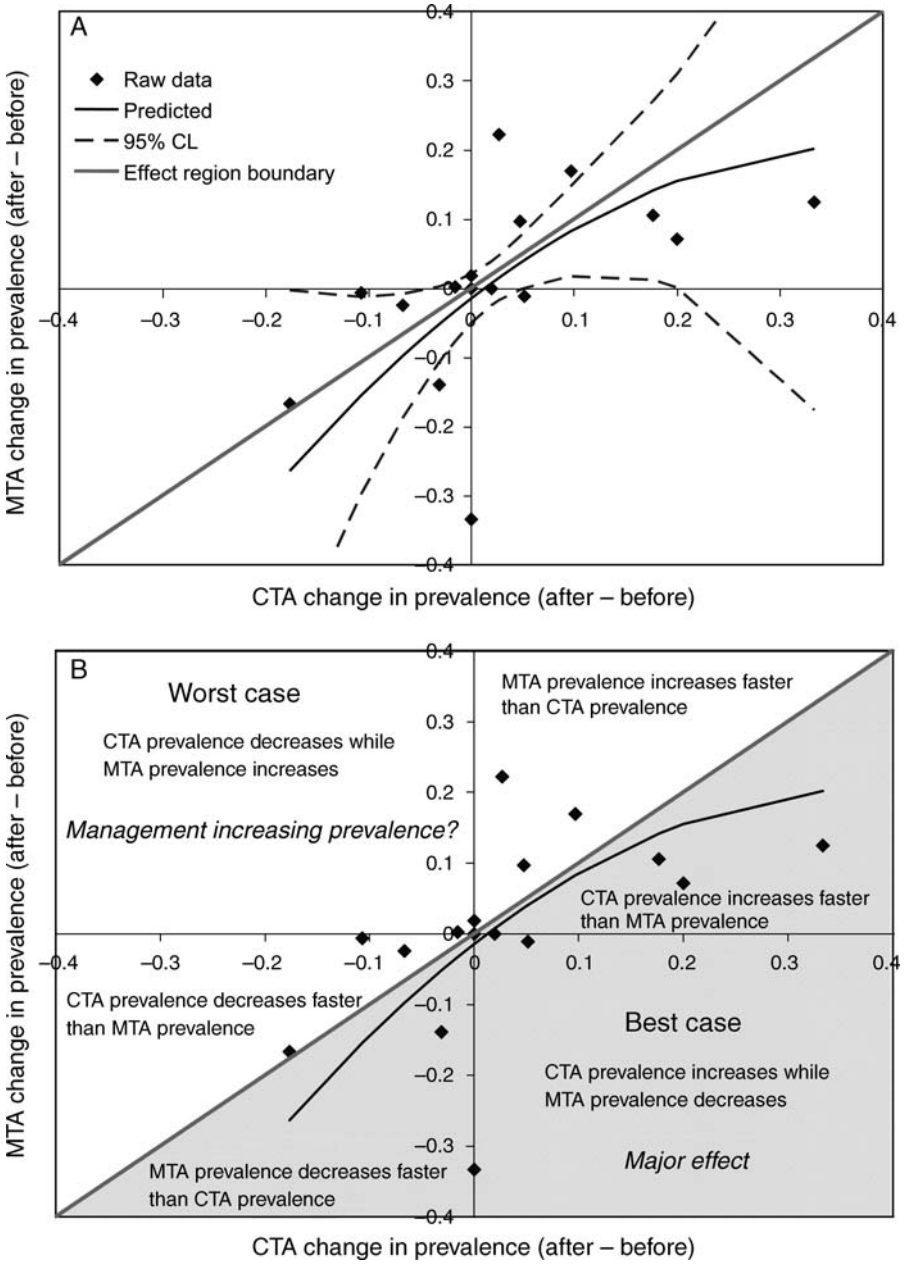

FIG. 3. (A) Quadratic curve of change (after – before) in chronic wasting disease (CWD) prevalence in mule deer on management treatment areas (MTA) vs. change on their spatially paired control treatment areas (CTA), weighted by the variance of the effect size. (B) The shaded region indicates, qualitatively, where management actions have an effect. Prevalence was estimated from surveillance data collected in Colorado, USA, from 1996 to 2005.

samples/yr would be required for the 5 site × 8-year collection scheme, or 144 samples/yr for the 6 site × 6-year scheme; in both cases, this equates to 12 samples/yr for each MTA and CTA. For the same power, sampling schemes, and relative drop, 400 and 500 samples/yr would be required if each site were considered separately, which breaks down to 40–42 samples/yr for each MTA and CTA. For the same power and sampling schemes but a 5% relative drop, 420 and 450 samples/yr (38–42 samples/yr for each MTA and CTA) would be required for a meta-analysis and >1400 samples/yr (>140 samples/yr for each MTA and CTA) regardless of sampling scheme if the analysis was run separately for each site (results not shown).

DISCUSSION

"One of the guiding precepts in field ecology is that no two areas are ever exactly alike, and it follows that no

two populations will be identical, either in numbers or in respect to other essential parameters." (Eberhardt 1976). In attempting to assess the effects of focal culling to control chronic wasting disease (CWD), we also faced this dilemma: we knew our management evaluation sites had variable environmental qualities and differences in mule deer abundance and management, and that there was also likely a high degree of innate spatial heterogeneity in the essential response variable, CWD prevalence (Miller et al. 2000, Conner and Miller 2004, Miller and Conner 2005). To address this site-to-site variation, we used spatial cluster and home range methods to delimit treatment and control areas for each site of management intervention, and estimated effect size for each area independently. We then analyzed effect sizes for these disparate sites together in a meta-analysis approach, which was more powerful than considering the effect at each site separately. Perhaps most importantly, this approach afforded the opportunity to use site-to-site variability in meta-analysis models to evaluate ecological and management hypotheses about CWD.

Our methods for delimiting treatment and control areas are broadly applicable to other wildlife and disease situations. When true experimental sites cannot be randomly selected a priori, because of management or other constraints, then researchers must use alternative methods to locate or define these sites. Cluster analysis can accomplish this by placing observations into groups as suggested by spatial (or other) arrangement of the data itself. These "natural" or "real" groups then can be modified in any number of ways to meet study-specific needs. In our study, natural clusters of disease management culls were used to discover treatment cores, and a buffer was applied to these cores to account for mule deer movement. A data-driven approach like this may be particularly suitable to wildlife disease problems where adequate georeferenced surveillance data are collected prior to management action.

As an application example, disease surveillance for West Nile virus has resulted in large sets of georeferenced data on human cases and status of nonhuman vectors (Brownstein et al. 2004); mosquito abatement has been widely used for intervention (Rainham 2005). Our methods could be used to identify and delimit abatement treatment and control areas, and a subsequent meta-analysis could be performed to evaluate effect size such as reduction in prevalence or incidence among nonhuman vectors (Brownstein et al. 2004), sentinel wildlife species such as crows (*Corvus brachyrhynchos*; Eidson et al. 2001, Julian et al. 2002), or species of concern, such as sage-grouse (Naugle et al. 2004). Oral delivery of rabies vaccination to raccoons (MacInnes 2000, Rosatte et al. 2001) or red foxes (Smith and Wilkinson 2003, Selhorst et al. 2005) are examples of other interventions for a disease with ample surveillance data that could readily adopt these methods. In such situations, selecting treatment and control areas beforehand is often difficult because the location, spatial extent, and timing of the management action are typically based on post hoc case-control analysis of disease "hot spots," or driven by political and logistical considerations. Thus, cluster analysis of the data to locate "hot spots" of disease can be used to locate high prevalence areas to target for management intervention, or to identify foci of management intervention.

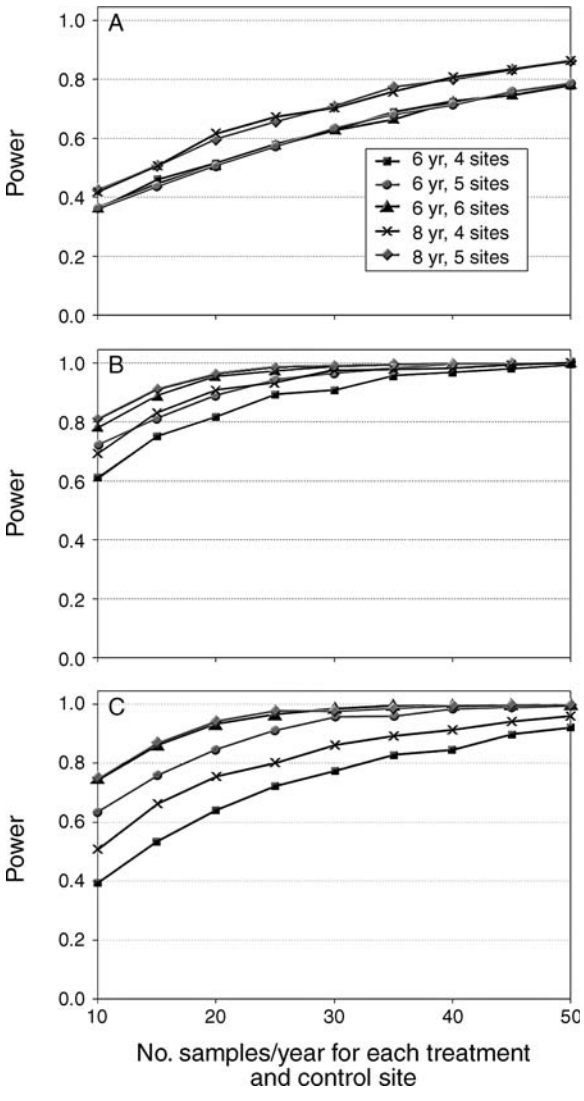

FIG. 4. Power for most efficient (i.e., lowest sample sizes) data collection strategies to detect a 10% relative drop in chronic wasting disease prevalence (i.e., change from 15% to 5% prevalence in MTA with no accompanying prevalence change in CTA) based on (A) analyzing data separately for each site, (B) using a meta-analysis approach and a paired *t* test, or (C) using a meta-analysis approach and nonparametric Wilcoxon paired-sample test.

We used a BACI analysis because our treatments were not randomly assigned (Eberhardt 1976, Green 1979), and we used a meta-analysis to combine data from many sites to achieve greater power and for its potential to

investigate sources of variation, such as intensity of culling or initial prevalence, otherwise unavailable from a single study (Franklin and Shenk 1995). The meta-BACI analysis provided a framework to examine replicated, multiple-site culling interventions over a wide range of conditions. The motivation for our analysis was to assess the success of a specific management intervention (culling) and, if possible, to do further analysis using environmental, biological, or management covariates to understand which factors might functionally relate to effect size (Boyce et al. 2005).

Following this logic (although we doubted that effect sizes were large enough to warrant continued analysis), we attempted to evaluate whether number of deer removed or prevalence of those removed was positively related to effect size. We constructed two models regressing relative drop on each site against the log of total number of deer removed and the prevalence in the management samples to evaluate which strategy appeared to be the most effective. Using a variance weighted regression, neither variable was significant (model df = 1, error df = 13, slope parameters $\beta = -0.021$, $P(\beta > 0) = 0.915$ and $\beta = -0.332$, $P(\beta > 0) = 0.955$, respectively), the trend was in the "wrong" direction (i.e., more deer removed or higher prevalence in the culled samples lead to a reduced effect), and the coefficients of determination were low ($R^2_{adj} = 0.073$ and 0.059, respectively). However, covariates may be more informative when there are a higher proportion of sites with significant results and/or larger sample sizes. This general meta-BACI approach is applicable to other wildlife management situations.

When data are collected over a longer time frame (e.g., more than five years for before and after periods), we recommend using a BACI design with samples paired in time rather than averaged across time, as done here due to low sample sizes (Stewart-Oaten et al. 1986). We further recommend using a random effects model and its associated shrinkage estimator (also called an empirical Bayes estimator). This approach attempts to remove sampling variation from the overall variance (Burnham et al. 1987, Johnson 1989, Ver Hoef 1996, Burnham and White 2002). Random effects models that treat the temporal variation as random with an average value have demonstrated excellent performance with high accuracy and precision (Link and Nichols 1994, Burnham and White 2002); this technique has also been applied to spatial variation (Johnson 1989, Ver Hoef 1996) and is easily expandable to a meta-BACI approach.

There are several possible reasons for the failure to demonstrate that culling affected CWD prevalence. The most parsimonious explanation is that the management prescription simply did not work. For seven of the 16 management evaluation sites included in our analyses, none of the culled deer were infected with CWD (Table 1), and consequently there was no direct effect of these removals on disease occurrence. Epidemic models suggest that nonselective removals might not effect rapid reductions in CWD prevalence in mule deer populations (Gross and Miller 2001), and thus the treatment may have been inadequate or the timeframe for assessment too short to discern effects. Ineffectiveness also could have been a result of insufficient or inconsistent removal of infected deer; wide variation in both numbers of deer removed and CWD prevalence among removals clearly occurred across sites (Table 1). However, regression analysis found no relationship between these two covariates and effect size.

Our necessary focus on measuring prevalence changes in male deer as a response variable also could have contributed to failure to detect management effects. Culling primarily targeted mature female deer, but because few data on females were available prior to 2001, we measured prevalence responses among males. If there were little contact between the sexes, then measuring males may have missed detecting an effect. However, mule deer biology suggests that risk of CWD infection in male mule deer may be associated with prevalence in females for several reasons. First, Koutnik (1981) found that males have seven times more social interactions than females over the course of a year. This may increase their probability of direct contact with CWD-infected females in the area. Additionally, male mule deer have been observed to wander from their home ranges more than females wander (Dasmann and Taber 1956) and, in one study (although small sample sizes plague the interpretation), males were found to have median home range sizes 6–8 times larger than those of females (Kufeld and Bowden 1995). In addition, we have observed, during the past 10 years of fieldwork in north-central Colorado, that movements of marked male mule deer encompass the ranges of many female groups. Wide-ranging movements may increase the probability that males come into indirect contact with prions in the environment. Lastly, and potentially most importantly, during the breeding season, mature male mule deer practice serial polygyny, and breeding males canvas as many females as possible by sniffing and licking the vulva of females to detect estrus (Geist 1981). We speculate that these behaviors may increase their contact with the infectious agent and, accordingly, the risk of contracting CWD (Miller and Conner 2005). It follows that female removal is potentially a viable strategy for reducing exposure risk for males, and that reducing the number of infected females locally could have lowered prevalence among males.

The relatively long course of CWD infection in mule deer (Williams and Miller 2002) could have contributed to lags in system response and thereby dampened management effects; however, because preclinical CWD infections can be detected relatively early in the disease course using the diagnostic methods employed here (Sigurdson et al. 1999, Miller et al. 2000, Miller and Williams 2002, Williams and Miller 2002, Williams

2005), lags in the detection of newly infected deer would likely span fractions of a year at most. The lag of approximately 0.7 year built into our original analysis would be more than adequate to cover delays attributable to newly infected animals. Moreover, including a lag of two years or more did not change the outcome of analyses. It is possible, however, that indirect prion transmission might at least partially uncouple survival of infected deer from epidemic dynamics (Miller et al. 2004), and could have diminished the short-term effects of culling on disease transmission within the timeframes studied here.

Alternatively, the failure to demonstrate management effects on CWD prevalence could have been a result of flawed "design." Although we were able to adhere to most relevant aspects of the BACI design, sample sizes were inadequate on some management evaluation sites (e.g., 16, 17, and 19). When management began in 2001, it was assumed that male and female samples would be grouped for prevalence estimation because differences between sexes had not been definitively demonstrated (Miller et al. 2000); however, subsequent work has shown dramatic differences in CWD prevalence between sexes for both mule deer (Miller and Conner 2005) and white-tailed deer (Grear et al. 2006). Consequently, sample sizes were lower than expected because females were inconsistently sampled within and among sites and it was clearly inappropriate to pool data from males and females. In addition, because hundreds of surveillance samples were being collected in the general vicinity of most management evaluation sites, sample sizes were not thought to be limiting; however, explicitly delineating and tallying available samples early on would have revealed that relatively few samples fell by chance within specific MTAs and CTAs. An initial power analysis would have motivated us to more fully consider these issues; this was a missed opportunity not atypical of large-scale field experiments (Aldridge et al. 2004). Moreover, the specific management actions under study were applied against a backdrop of ongoing deer population management activities that changed over the course of the study period. In 2001, female harvest was substantially increased in the Game Management Units (containing many of the management evaluation sites studied here) in a broader attempt to reduce the size of infected herds. Although the general trend was for increasing CWD prevalence during this period in north-central Colorado (Miller and Conner 2005), deer abundance probably was not reduced uniformly, and thus the overarching management prescription could have reduced local CWD prevalence on MTAs and CTAs independent of culling; if these effects were not uniform, then culling-related effects may have been confounded.

As often happens in resource management situations (Marcot 1998), Colorado Division of Wildlife (CDOW) managers faced with enacting a pioneering program to control CWD were constrained by political, social, and logistical aspects of the interventions under consideration. And, consideration was not fully given to the details of the design of the management experiment (e.g., spatial area of effect and resultant sample size). In retrospect, explicitly considering all of the aspects of design described here would have resulted in an altered design, but not necessarily increased sample requirements, as illustrated by our post hoc power simulations. With adequate time (and better preliminary data), we could have chosen experimental sites with appropriate pre-intervention sample sizes and optimally allocated post-intervention data collection efforts to provide statistically adequate sample sizes for detecting a 10% relative drop in prevalence. From our post hoc power analyses, we estimated only 12 samples/yr (for each relevant age and sex class) were needed from each MTA and CTA, numbers that could have been collected easily and without extra expense; sampling in CTAs could have been augmented with live-animal testing (Wolfe et al. 2002, 2004) to minimize potential confounding effects of harvest-based sampling on effects arising from management removals. One element missing from our simulation is the temporal form that a management-induced decrease in CWD might take. There could be a treatment threshold to reach before CWD prevalence drops, such that many years might pass before any decline in prevalence occurs. These possible processes, presently undescribed, were not included in the power simulation. Thus although simulation modeling helps guide or frame monitoring design, in the absence of such biological insights it may be prudent to err on the side of selecting longer "after" periods for evaluating management actions where sufficient social and political tolerance can be secured.

As illustrated by our experience, future wildlife disease management experiments would benefit from planning that includes explicitly delineating spatial effect areas before beginning intervention and, even when dealing with seemingly large sample sizes, conducting power simulations to define data needs. Following these recommendations, cluster analysis used in tandem with biologically relevant spatial delineation of treatment and paired control areas, coupled with a meta-BACI analysis, provides a powerful approach for evaluating effects of management interventions using disease surveillance data.

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