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SURVEILLANCE TO DETECT CHRONIC WASTING DISEASE IN WHITE-TAILED DEER IN WISCONSIN

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ABSTRACT: Chronic wasting disease (CWD), a prion disease affecting North American cervids, has been discovered in at least 12 states and provinces throughout the continent. Since 2002, a number of states and provinces have initiated surveillance programs to detect CWD in native cervid populations. However, many questions remain about the appropriate methods, geographic scope, and number of samples required for an effective CWD surveillance program. We provide an improved statistical method to calculate the probability of detecting CWD in primary sample units (e.g., county or deer management unit) that also considers deer abundance and the nonrandom distribution of CWD and hunter harvests. We used this method to analyze data from a statewide CWD detection program conducted in Wisconsin during the autumns of 2002 and 2003 to determine the distribution of CWD in white-tailed deer (*Odocoileus virginianus*). Deer heads were collected at hunter registration stations, and brainstem (obex) and retropharyngeal lymph nodes were removed for disease testing. Our analysis includes samples from >35,000 deer collected outside the known affected area. The probability of detecting chronic wasting disease at a prevalence of 1% varied from 0.89 to ≥0.99 among the 56 primary sample units. Detection probabilities for 1% CWD prevalence were >0.9 in 55 primary sample units, and >0.99 in 10. Detection probabilities will be higher in areas where CWD prevalence exceeds 1%. CWD-positive deer were detected in eight primary sample units surrounding the known affected area during surveillance activities. Our approach provides a novel statistical technique to accommodate nonrandom sampling in wildlife disease surveillance programs.

Key words: Chronic wasting disease, disease surveillance, *Odocoileus virginianus*, white-tailed deer, Wisconsin.

INTRODUCTION

Chronic wasting disease (CWD) is a fatal neurodegenerative disease of mule deer (*Odocoileus hemionus*), white-tailed deer (*Odocoileus virginianus*), and elk (*Cervus elaphus*) associated with the presence of transmissible protease-resistant prion proteins (PrP^{CWD}; see review by Williams et al., 2002). There is considerable uncertainty surrounding basic epidemiology of CWD, including the transmission route, factors affecting occurrence and prevalence, and mechanisms associated with introduction or spread of disease into new areas. Chronic wasting disease was first recognized in captive mule deer in Colorado in the 1960s (Williams and Young, 1980) and subsequently was described in free-ranging and captive cervids in several other states and provinces (Williams et al., 2002; Joly et al., 2003).

The presence of CWD is considered a long-term threat to free-ranging deer and elk populations (Gross and Miller, 2001) with an associated loss of recreational activity and economic benefits. As a result, surveillance to detect CWD has become an important component of many state and provincial wildlife management programs (Beringer et al., 2003; Samuel et al., 2003; Diefenbach et al., 2004). Surveillance can take a variety of forms ranging from targeted surveillance of clinical animals, testing of car-killed animals, to

geographically random sampling of harvested deer under rigorous statistical methodology (Samuel et al., 2003). Although surveillance based on opportunistic samples has been successful in detecting CWD, when disease has not been detected in a state or local area, rigorous statistical methods are necessary to determine the level of certainty that can be attributed to the surveillance program. In the absence of statistical estimation, there will be considerable uncertainty about whether the disease is likely to be present in an area and was simply not detected because the surveillance program was inadequate. The current geographic distribution of CWD, and therefore the scale of the management problem, is not well known because in many cases surveillance has been inadequate to detect early CWD infections at the state or local level. Improved knowledge of the distribution of CWD and reliable assessment of the probability of detecting disease is important in reducing our uncertainty about the geographic distribution of disease, for developing appropriate management strategies, and in understanding risk factors associated with disease spread.

Disease detection based on statistical sample survey methods typically assumes that all animals in the target population are randomly sampled (e.g., Nusser et al., 2008). Specifically, each individual in the population is assumed to be equally likely to be sampled and tested. However, several epidemiologic and ecologic factors likely cause violation of this assumption. We elaborate on this topic below; however, spatial aggregation of infected individuals and sampling effort are two common ways that random sampling is violated (Samuel et al., 2003). As with most newly emerging infectious or transmissible diseases in wildlife, CWD is unlikely to be distributed randomly through a population; there will be focal areas of infection or greater prevalence (Farnsworth et al., 2006; Joly et al., 2006). Further, variation in hunter access, terrain, and human population densities, among other factors, will likely result in spatial variation in sampling effort wherein some areas are overrepresented in the sample, whereas other areas are underrepresented (Nusser et al., 2008). Consequently, statistical methods that accommodate this spatial variation in disease and sampling effort are necessary for analysis of wildlife disease surveillance data.

Following the discovery of CWD in Wisconsin, the Department of Natural Resources (WDNR) implemented a comprehensive CWD management strategy, with surveillance, management, and research components (Bartelt et al., 2003). As part of this comprehensive plan, the WDNR undertook a statewide surveillance program in the autumns of 2002 and 2003 to determine the distribution of CWD in Wisconsin white-tailed deer. The objectives of our research were to develop improved statistical methods for estimating the probability of detecting early outbreaks ($\leq$1% prevalence) of a wildlife disease that is likely to be locally clustered such as CWD, by using data from deer harvested by hunters. To achieve improved statistical estimates of detection probability we applied these methods to smaller areas within deer management units and/or counties in Wisconsin. Results of these surveillance efforts have been crucial to determine the likely distribution of CWD in Wisconsin and shaping CWD management response.

MATERIALS AND METHODS

Surveillance design

Several decisions must be made when designing a statistically based surveillance strategy to detect the presence of disease. First, for a disease outbreak, managers should establish a goal for the minimum detectable prevalence (MDP; adapted from "minimum expected prevalence"; Cameron and Baldock, 1998a, b); where MDP represents the minimum prevalence (or minimum detectable probability of infection) that is desired to be detected during surveillance. Second, the geographic extent of the outbreak or area of

surveillance and discrete sampling units must be defined. Standard statistical methods have been developed for livestock, where animals are distributed in discrete herds that can be enumerated and randomly sampled, to assess "herd prevalence" (minimum proportion of herds that are affected) before the disease is detected (Cameron and Baldock, 1998b), but this concept has little meaning for free-ranging cervids, which do not occur in discrete and exclusive herds that can be randomly selected for sampling. For most wildlife populations it will be more useful to define a minimum detectable area (MDA) of the CWD outbreak; in practice this could represent a geographic management area or a discrete subpopulation unit. Third, the desired probability of detecting the hypothetic outbreak is chosen, which will dictate sample-size requirements. Objectives for managing the disease, if detected, should be considered when making each of these decisions (Samuel et al., 2003). For example, if the management goal is disease eradication, then achieving that goal is maximized through a surveillance strategy that has a high probability of detecting an early outbreak of low prevalence that is confined to a small geographic area. Financial and logistic considerations will impose practical constraints on the ability to meet ideal surveillance objectives, and consequently post-hoc analysis may be required to assess the probability of detecting a CWD outbreak with a particular prevalence, distributed over a particular area, based on a previously collected sample of animals.

The surveillance program using hunter-harvested deer in Wisconsin was planned with sufficient samples to achieve 0.99 probability of detecting CWD at an MDP of 1% in deer >1 yr old in each of 56 primary sampling units (PSU) throughout the state. For the surveillance program we defined a PSU as 1) a deer management unit (DMU; or group of DMUs) adjacent to the known affected area (mean area 1,602 km^2, $n=8$), or 2) a county (or multiple counties where deer numbers were low) in the remainder of the state (mean area 2,725 km^2, $n=48$). Initially, we assumed that disease and deer harvest would be randomly distributed with respect to the deer population, and established a target sample size of 500 deer for each primary sampling unit (following Cannon and Roe, 1982).

Sample collection

Heads from deer >1 yr of age were collected from hunters at 200 check stations used for mandatory registration of hunter-harvested deer throughout the state during the autumns of 2002 and 2003. Although sampling was primarily conducted statewide in 2002, additional samples were collected from underrepresented sampling units in 2003, based on a preliminary examination of the 2002 data. CWD-positive deer were discovered in some PSUs the first year. Therefore, detection probability for these PSUs was calculated with the use of the samples from the first year (2002). An attempt was made to collect samples throughout each sampling unit to avoid overrepresentation of some areas and underrepresentation of others. Not all deer that were brought to the registration station were sampled. Hunters were interviewed to determine the location of kill recorded to the Public Land Survey System township (93 km^2). In addition to location of kill, the age, sex, and date of kill, and contact information for each hunter were also collected.

In 2002, immunohistochemical (IHC) staining was used to detect the presence of protease-resistant protein, PrP^{cwd} (Miller and Williams, 2002; Keane et al., 2008). In 2003, some deer were tested with the use of IHC staining, but most were tested using an enzyme-linked immunosorbent assay (ELISA)–based screening test (IDEXX; D. Keane, Wisconsin Veterinary Diagnostic Laboratory, unpubl. data) on frozen lymph nodes, with initial positives confirmed by IHC. In both years retropharyngeal lymph nodes were tested first; if positive, IHC was conducted on lymph node and obex. Deer for which PrP^{cwd} was detected by IHC in retropharyngeal lymph nodes or obex were considered CWD-positive (Miller and Williams, 2002; Joly et al., 2003). We excluded from analysis 1,346 <1-yr-old deer because of very low prevalence in that age class (Grear et al., 2006).

Deer abundance

Deer abundance (sample population) for each PSU is not typically known for most deer populations. We estimated the fall 2002 prehunt deer population size for each PSU with the use of the sex-age-kill (SAK) method (Creed et al., 1984), which is used in Wisconsin and other states to monitor deer populations. SAK produces generally unbiased deer estimates for populations with a stable sex–age composition and relatively stationary abundance (e.g., $\lambda=0.95$–1.05), but low population estimates for stable and increasing populations (Millspaugh et al., 2006), the two most likely situations in Wisconsin. Precision of the SAK population estimates depend on demographic stochasticity, sampling variation,

and total population size (Millspaugh et al., 2006). We used the SAK method to estimate deer abundance in each PSU; however, as deer were not randomly distributed within the PSUs, we estimated the number of deer in each township by assuming that the deer abundance in the PSU was distributed in relative proportion to deer range (i.e., the proportion of the deer in each township was equal to the proportion of deer range). Deer range for the entire state of Wisconsin was mapped with the use of a geographic information system, and was defined as: 1) forest, shrub land, and wetland >4 hectares; 2) forest, shrub land, and wetland >1 hectare within 200 meters of larger tracts of the same; and 3) agriculture and grassland within 100 m of forest, shrub land, and wetland. Mean estimated deer abundance per PSU was 25,500 (SD=10,100).

Calculation of CWD detection probabilities

The expected number of CWD-positive deer in a primary sampling unit (PSU) at MDP is determined by

$$d = \text{MDP} \times N, \tag{1}$$

where N is the total number of deer in a PSU. If d positive deer and n samples are completely spatially randomly (CSR) distributed within the PSU, the probability of finding ≥1 positive in the PSU by testing samples would be calculated as (Cannon and Roe, 1982):

$$P_{\text{CSR}} = 1\text{-}(1\text{-MDP})^n. \tag{2}$$

This calculation assumes an infinite population size (Cannon and Roe, 1982), and therefore is conservative (i.e., underestimates detection probability). Cannon and Roe (1982) provide alternative formulae when the population size is known.

Hunter harvest likely does not constitute a spatially random sample of a population within a large area (e.g., units of 1,500–3,000 km^2 in our study). In addition, the infectious nature of CWD makes a clustered distribution on the landscape likely (Miller et al., 2000; Farnsworth et al., 2006; Joly et al., 2006). Such spatially nonrandom sampling and disease risk can cause overestimation of the true detection probability (Samuel et al., 2003). However, this overestimate can be reduced by using a more limited scale (e.g., township, 93 km^2) where spatially random sampling and disease distribution are more likely. We assumed that harvested deer were sampled at random within each township, and calculated the probability of detecting ≥1 CWD-positive deer in a township (P_t) with the use of the binomial approximation:

$$P_t = 1\text{-}(1\text{-}p_t)^{n_t}, \tag{3}$$

where p_t (Eq. 5) and n_t are the prevalence and number of samples from township t within a PSU, respectively.

In Wisconsin, the spatial distribution of an early CWD outbreak (i.e., the MDA) will likely be smaller than a PSU, probably multiple townships in size (e.g., Joly et al., 2006). We typically used an MDA consisting of four adjacent townships; however, because of irregular PSU boundaries the actual area varied from two to seven adjacent townships. These MDAs may be referred to as "clusters" in the survey sampling literature (Thompson, 2002; Nusser et al., 2008). The probability of detecting CWD in an MDA (P_m) is the complement of the joint probability that no CWD is found in any township t within the MDA:

$$P_m = 1\text{-}\prod_{t=1}^{T}(1\text{-}P_t) = 1\text{-}\prod_{t=1}^{T}(1\text{-}p_t)^{n_t}, \tag{4}$$

where T is the number of townships in MDA m. We assumed that all d positive deer in the PSU would be randomly distributed within the MDA. The prevalence in each township (p_t in Eq. 3) is estimated by

$$p_t = d/N_m, \tag{5}$$

where N_m is the estimated number of deer in MDA m (assuming prevalence is uniform throughout the MDA). Assuming all the positive deer (d) are found in a single MDA, prevalence in the affected MDA will be greater than expected for the entire PSU (p_t>MDP). The probability of detecting CWD in each MDA within a PSU is the joint probability that the MDA has all CWD-positive deer (P_m^+), and the probability of detecting CWD in the MDA given that it is present (Eq. 4). The current lack of understanding of factors related to local patterns of CWD infection prevents direct calculation of the values of P_m^+; however, as a logical starting point we assumed that the probability of an MDA having CWD-positive deer is determined by the relative abundance of deer in the MDA:

$$P_m^+ = N_m/N. \tag{6}$$

We note that alternative approaches for calculating P_m^+ are possible depending on knowledge about the factors affecting CWD risk (Samuel et al., 2003; Conner et al., 2007). For example, alternatives might include estimating P_m^+ as a function of the number of MDAs in the PSU (1/

M) or as a function of the relative number of infected game farms in the MDA.

To calculate the probability of detecting CWD in a PSU, we assumed that during early phases of an outbreaks (when disease is rare) CWD would not occur in >1 MDA. Following the law of total probability, the probability of detecting CWD in a PSU is the sum of mutually exclusive detection probabilities for each MDA (Pr[detecting CWD in MDA|CWD present] Pr[CWD present in MDA]) in the PSU:

$$P=\sum_{m=1}^{M}\left(P_m^{+}\times P_m\right), \tag{7}$$

where M is the number of MDAs in the PSU.

To examine the effect of spatial nonrandomness among samples, we examined the difference between our estimate for P (Eq. 7) and the probability of detecting CWD in a PSU based on the typical assumption of CSR in sampling (e.g., a spatially uniform or nonclustered sample) and 1% disease prevalence (MDP=0.01) at the PSU level:

$$P_{\mathrm{CSR}}=1\text{-}(1\text{-}0.01)^{n}, \tag{8}$$

where n is the number of samples in the PSU. We then estimated the degree of sample aggregation in a PSU with the use of Green's coefficient of dispersion C (a common measure of aggregation where negative, zero, and positive values indicate uniform, random, and aggregated distributions respectively; Green, 1966). Green's C was calculated as

$$C_{\mathrm{PSU}}=\left\{\left[s^2\Big/\left(\sum n_t\Big/T\right)\right]\text{-}1\right\}\Big/\left(\sum n_t\text{-}1\right), \tag{9}$$

where s^2 is the variance in number of samples among townships in a PSU, and n_t and T are defined as above. As sampling effort changed in the second year of the study (where sampling was targeted to increase sample sizes in underrepresented areas), we conducted this analysis only using the 2002 data. Furthermore, as sampling intensity was much greater in the eight higher-risk PSUs around the known affected area (these units were much smaller and had larger sample sizes), we conducted this analysis both excluding and including these units, as this increased sampling effort may have overwhelmed any inherent spatial aggregation in the sample. We predicted a positive relationship between spatial aggregation (Green's C) and the difference between P and P_{CSR}.

The number of animals in any wildlife population is rarely known, and many alternative methods are typically used to estimate abundance (e.g., Skalski et al., 2005). However, standard statistical calculations of disease detection probability (P) usually assume the total population is fixed (N), rather than estimated with uncertainty ($\hat{N}$). We conducted computer simulations to evaluate how variation in the estimated population affected the probability of disease detection (P). For each simulation we fixed the true population (N) and minimum detectable prevalence (MDP), and calculated the number of infected individuals (d) in the true population. We then generated an estimated population ($\hat{N}$) with the use of a coefficient of variation (CV) that ranged between 5% and 15% ($\hat{N}=N\pm 2\text{*}\mathrm{CV}\text{*}N$). Simulations were replicated 100,000 times for each of 250 combinations of true population sizes (5,000–50,000), CV (5–15%), and MDP values (1–5%). For each of these 250 combinations we calculated average $\hat{\mathrm{MDP}}=d/\hat{N}$, bias, and mean square error (MSE) of $\hat{\mathrm{MDP}}$. We used $\hat{\mathrm{MDP}}$ to estimate how P_{CSR} (Eq. 7) was affected for a range of n (50, 100, 200, and 300), and by simple inference the affect on P (Eq. 7). Three of the 250 combinations produced estimates of MSE that seemed unreliable and were not used in our evaluation.

RESULTS

Throughout Wisconsin, 35,080 deer were tested during both years of harvest. On average there were 626 deer tested per PSU (SD=433, n=56). Detection probabilities (P) for 1% CWD prevalence were high for most PSUs, ranging from 0.89 in Crawford county in the southwest to >0.99 in the PSUs near the CWD affected area (Fig. 1). Adjacent to the CWD-affected area, the detection probability goal of 0.99 was met in six PSUs, whereas the remaining two had detection probabilities >0.95. In the remainder of the state, detection probabilities were 0.9–0.99 in 47 of the 48 PSU; only one was less than 0.9 and the goal of 0.99 was met in four PSUs. CWD-positive deer were discovered in six of eight PSUs adjacent to the CWD-affected areas; four PSUs each year (Fig. 1). Further, CWD-positive deer were found in two PSUs in the southeastern portion of the state (Fig. 1).

Estimates for P_{CSR} in 2002 were $\geq P$ in all cases. The average difference was 0.028

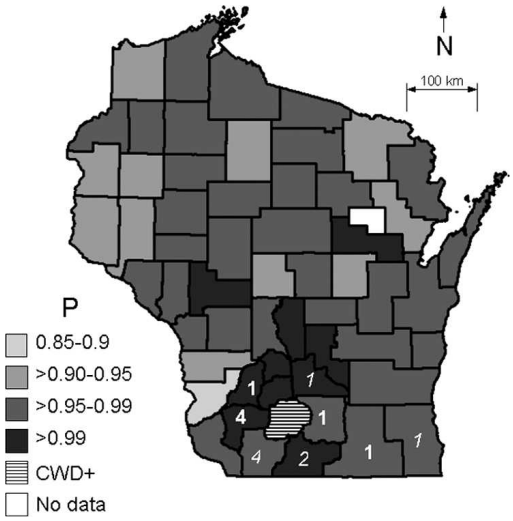

FIGURE 1. Probability of detecting chronic wasting disease in Wisconsin (P) by primary sample unit assuming a minimum detectable prevalence of 1%, distributed in a minimum detectable area of approximately four townships (ca. 372 km^2). The striped area in south-central Wisconsin was the known affected area in September, 2002, and the white area indicates Menominee Country, from which no samples were available. Numbers indicate number of CWD-positive deer found during the 2002/2003 (bold) and 2003/2004 (italic) hunting seasons.

(SD 0.027, n=56) and ranged from 0 to 0.105. Differences were positively correlated with aggregation of samples in townships among PSUs (as indexed by Green's C) regardless of whether the eight PSUs adjacent to the known affected area were excluded (Pearson's product moment correlation coefficient, r=0.37, t=2.74, p=0.009) or included (Pearson's product moment correlation coefficient, r=0.25, t=1.93, p=0.059).

Average MDP from our computer simulations was typically larger than the true MDP by 5–6% and nearly always (96%) by <15%. The amount of this bias and magnitude of MSE increased with higher CVs for the estimated population size ($\hat{N}$) and for higher values of true MDP, but not for N. Our results indicate that uncertainty about the true population size of animals being sampled in a PSU (or other sampling unit) will usually overestimate the number of infected animals (d) and MDP. These factors contribute to overestimating P_{CSR} by an average of ≤0.02 with more bias occurring when true P_{CSR}<0.9 and very little bias when P_{CSR}>0.9, likely because n is then sufficient for even large populations (>25,000). In a few simulations with small MDP (≤1%), high population variance (CV≥15%), and small sample size (n≤100) probability of disease detection was overestimated by >0.05. This problem of slightly overestimating detection probability affects both P and P_{CSR} whenever population size is not precisely known. Because the size of wildlife populations is seldom known precisely, there is a need for development of methods of estimating disease detection that consider the effect of population uncertainty and bias.

DISCUSSION

Analysis of surveillance data typically requires random sampling and random disease distribution at the scale of the PSU. It is unlikely that either assumption is satisfied in samples derived from hunter harvest or during early stages of an infectious disease outbreak. Because spatial autocorrelation in sampling and disease distribution can result in a reduction in detection probability (Samuel et al., 2003), assuming randomness typically results in an overestimate of detection probability, as shown by our analysis. However, using smaller sampling units where violation of the assumptions of random sampling and disease distribution is less severe may reduce the degree of bias in the estimated detection probability. For example, we found that detection probabilities estimated by assuming spatial randomness at the PSU level (approximately 4–11 times larger than our MDA) were higher by as much as 0.105 compared with assuming randomness at the township level (approximately 1/7 to 1/2 the size of our MDA). We believe that

larger PSUs can exaggerate the bias in detection probability primarily because of nonrandom disease distribution. In particular, large PSUs (e.g., an entire state or region) could severely overestimate the probability of detecting CWD until the disease becomes widely distributed or reaches high local prevalence. In general, using smaller, ecologically based sampling units (or MDAs) should reduce bias in detection probability calculations from spatially nonrandom sampling and disease distributions. A potential problem in all wildlife disease surveillance studies is the variation (and sometimes bias) associated with estimating the size of the population being evaluated. This uncertainty is likely to result in a small overestimation of the detection probability achieved by the surveillance program. As a result, we suggest that managers test a sufficient number of animals to ensure >90% detection probability, which minimizes this potential bias. When detection probability is much lower (<80%) and population estimates have a high uncertainty (CV>10%) we suggest that estimated detection probabilities be considered with some caution.

Our approach assumes that disease is clustered into a single MDA within the PSU. This assumption is most likely correct for clustered diseases (such as CWD) when surveillance occurs during the early phase of a disease outbreak. Fortunately, these conditions are most likely to be met when adequate surveillance is conducted, but disease has not been detected. If disease becomes more widely distributed (less clustered and more spatially random), infected animals are likely to be more abundant and occur in >1 MDA. When investigators believe this situation is likely, we recommend appropriate adjustments in the distribution of the expected number of infected individuals (d) into >1 randomly sampled spatial areas, such as townships (Eq. 5).

Many state and provincial agencies use a combination of active and opportunistic (i.e., sampling of clinical suspects) approaches for CWD surveillance (Conner et al., 2000; Miller et al., 2000; Joly et al., 2003). Opportunistic surveillance programs are less expensive overall and can also be applied where hunting is prohibited, and thus are an attractive option for surveillance (e.g., Samuel et al., 2003). Although any CWD detection program is capable of identifying CWD-positive animals, sampling the entire population at risk is required to calculate detection probabilities and prevalence. Critical parameters necessary to use opportunistic surveillance to calculate population-level detection probabilities, including case-ascertainment and case-reporting rates (Doherr and Audige, 2001), prevalence of clinical signs in the population, and proportion of CWD-positive individuals that are clinical (Samuel et al., 2003), are all currently unknown for CWD. Further, if a CWD-positive individual is found by sampling clinical suspects, additional surveillance activities are necessary to estimate local prevalence and extent of disease before management decisions can be made. Therefore, we suggest wildlife management agencies rely on a dual strategy of testing clinical suspects and sampling of hunter-collected deer and elk for detection for CWD (Conner et al., 2000; Miller et al., 2000), but make necessary adjustments in analysis of the hunter-derived data for potential nonrandom sampling and local disease clustering based on methods presented herein or by alternative model simulation approaches (Nusser et al., 2008).

In applying our approach, others should consider the behavior, movement patterns, and population boundaries of cervids being sampled. For example, an assumption of random sampling and disease distribution at the township level may be an unnecessarily restrictive assumption for migratory elk or deer, depending on the distances moved (e.g., Conner and Miller, 2004). The PSU for

statistical analysis might more appropriately be set at the herd, subpopulation, or population level rather than a particular area.

Surveillance strategies to detect CWD should be designed to link closely with potential management objectives (Samuel et al., 2003). The prospect for eradication of CWD will be best if an outbreak is discovered early, so sampling effort should be sufficient to detect as small an MDP and MDA as possible if eradication is the goal. Population simulation suggested that control of CWD with the use of selective culling of affected individuals was more often achieved when prevalence was <1% (Gross and Miller, 2001). Less sampling effort will be necessary for less aggressive management programs, where the goal may be simply to monitor disease distribution once it is discovered. In general, management agencies should carefully consider the potential management actions that will be enacted if CWD is discovered, as early as possible in design of CWD detection programs. Currently, there are no specific guidelines about how long to conduct CWD surveillance or how frequently follow-up surveillance is needed to detect new disease foci (Samuel et al., 2003). Decisions about length and frequency of CWD surveillance likely depend on the risk of disease occurring, on management goals, and on the costs of conducting surveillance activities, which can be expensive.

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