

## DYNAMICS OF PRION DISEASE TRANSMISSION IN MULE DEER

MICHAEL W. MILLER,<sup>1,4</sup> N. THOMPSON HOBBS,<sup>2</sup> AND SIMON J. TAVENER<sup>3</sup>

<sup>1</sup>*Colorado Division of Wildlife, Wildlife Research Center, 317 West Prospect Road, Fort Collins, Colorado 80526 USA*

<sup>2</sup>*Department of Forest, Rangeland, and Watershed Stewardship and Natural Resource Ecology Laboratory, Colorado State University, Fort Collins, Colorado 80523-1499 USA*

<sup>3</sup>*Department of Mathematics, Colorado State University, Fort Collins, Colorado 80523-1874 USA*

**Abstract.** Chronic wasting disease (CWD), a contagious prion disease of the deer family, has the potential to severely harm deer populations and disrupt ecosystems where deer occur in abundance. Consequently, understanding the dynamics of this emerging infectious disease, and particularly the dynamics of its transmission, has emerged as an important challenge for contemporary ecologists and wildlife managers. Although CWD is contagious among deer, the relative importance of pathways for its transmission remains unclear. We developed seven competing models, and then used data from two CWD outbreaks in captive mule deer and model selection to compare them. We found that models portraying indirect transmission through the environment had 3.8 times more support in the data than models representing transmission by direct contact between infected and susceptible deer. Model-averaged estimates of the basic reproductive number ( $R_0$ ) were 1.3 or greater, indicating likely local persistence of CWD in natural populations under conditions resembling those we studied. Our findings demonstrate the apparent importance of indirect, environmental transmission in CWD and the challenges this presents for controlling the disease.

**Key words:** basic reproductive number ( $R_0$ ); chronic wasting disease (CWD); epidemic model; mule deer; *Odocoileus hemionus*; prion disease; transmissible spongiform encephalopathy.

### INTRODUCTION

Chronic wasting disease (CWD; Williams and Young 1980), an emerging prion disease of the deer family, has the potential to cause severe harm to deer (*Odocoileus* spp.) populations (Gross and Miller 2001, Williams et al. 2002) and thus to disrupt ecosystems where deer occur in abundance (Hobbs 1996). Because effective vaccines or therapies are lacking, control strategies for prion diseases rely on understanding and interrupting transmission pathways. Consequently, understanding how CWD is naturally transmitted has emerged as an important challenge for contemporary ecologists and wildlife managers. Although CWD is contagious among deer (Miller and Williams 2003), the relative importance of possible pathways for its transmission remains unclear. To better understand the likely importance of these potential pathways as a basis for assessing potential control strategies, we developed models representing competing hypotheses on CWD transmission and tested these using data from natural epidemics in captive mule deer (*Odocoileus hemionus*).

Animal prion diseases (Prusiner 1998) have been targeted for control or eradication worldwide (WHO 2000, Vallat 2003). Unfortunately, effective measures for controlling two animal prion diseases, CWD of deer (*Odocoileus* spp.) and wapiti (*Cervus elaphus nelsoni*), and scrapie of sheep and goats, remain elusive (Hoinville 1996, Williams et al. 2002, Baylis and McIntyre 2004). Control efforts have been hampered in part because both CWD and scrapie are contagious among susceptible hosts (Hoinville 1996, Miller and Williams 2003), and in part because transmission mechanisms remain incompletely understood. In contrast, a third important animal prion disease, bovine spongiform encephalopathy (BSE) in cattle, has been controlled much more effectively than has either CWD in cervids or scrapie in sheep and goats. Successful control of BSE is attributable in part to its lack of contagiousness, and in part to a clear understanding of how it is transmitted to cattle via contaminated feed (Wilesmith et al. 1991, Hoinville et al. 1995, Anderson et al. 1996).

Epidemics of CWD and scrapie are sustained largely by horizontal transmission (Woolhouse et al. 1998, Miller and Williams 2003). Both infected animals and environments contaminated with the causative agent can be sources of infection (Pálsson 1979, Hoinville 1996, Woolhouse et al. 1998, Miller and Williams 2003, Miller

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<sup>4</sup> E-mail: mike.miller@state.co.us



PLATE 1. Two natural epidemics of chronic wasting disease (CWD) in captive mule deer (*Odocoileus hemionus*) held at the Colorado Division of Wildlife's Foothills Wildlife Research Facility provided data on disease-related mortality patterns that we compared to model predictions to evaluate the relative support for each of seven competing models of prion transmission dynamics. Photo credit: M. W. Miller.

et al. 2004), and under some conditions infectious agent persists in the environment for years (Pálsson 1979, Miller et al. 2004). Direct (animal–animal) and indirect (animal–environment–animal) prion transmission have been incorporated into models used to study epidemic dynamics and control strategies (Woolhouse et al. 1998, Hagensaaers et al. 2000, Gross and Miller 2001); however, whether one mechanism or the other best represents natural transmission processes has not been discerned. Control strategies for contagious prion diseases have focused on infected live animals as the primary source of infection, but indirect transmission and environmental persistence of prions could greatly complicate control efforts by uncoupling disease transmission from the presence of infected animals.

Here we describe the development and comparison of models representing competing hypotheses on CWD transmission. Our simplest model portrayed direct transmission between infectious and susceptible individuals (Anderson and May 1979). Increasingly detailed models included direct transmission with a latent period preceding agent shedding, direct transmission with an incubation period preceding onset of disease-associated mortality, indirect transmission arising from an environmental pool of infectivity, indirect transmission with latency, and combined direct and indirect transmission. We then evaluated support for these competing models using data from two CWD epidemics in captive mule deer (see Plate 1).

## METHODS

We developed and compared six compartment models derived from the *SI* family of ordinary differential equations (the simplest of epidemic models, with only susceptible [*S*] and infected [*I*] subpopulations; Anderson and May 1979). Each model represents an alternative pathway for chronic wasting disease (CWD) transmission in mule deer. We evaluated these models with data from two epidemics in captive populations; a seventh model that relied exclusively on maternal transmission completely failed to mimic observed epidemic patterns (data not shown) and was not evaluated further. For all six models, we assumed that the number of infectious contacts per infected animal per unit time increased as population size increased (i.e., density-dependent transmission) (de Jong et al. 1995, McCallum et al. 2001, Begon et al. 2002). We made this assumption because the total area used by the captive populations we studied was constant; consequently, density increased as the population increased. Although the assumption of density-dependent transmission may be more tenuous in natural populations (de Jong et al. 1995, McCallum et al. 2001, Begon et al. 2002), frequency-dependent transmission, which assumes a constant density as population size increases, was clearly an inappropriate assumption for portraying epidemic dynamics in a population living in a fixed space.

The simplest model portrayed direct transmission between individuals:

$$\begin{aligned} \frac{dS}{dt} &= a - S(\beta I + m) \\ \frac{dI}{dt} &= \beta SI - I(\mu + m) \end{aligned}$$

where  $S$  is the number of susceptible animals,  $I$  is the number of infected animals,  $a$  is the number of susceptible animals annually added to the population via births or importation,  $m$  is the per capita natural mortality rate,  $\mu$  is the per capita CWD mortality rate (=1/clinical course, the average time between initial infection and death from the disease) and  $\beta$  is the CWD transmission coefficient (units = time<sup>-1</sup>).

Because there may be a period of latency during which infected animals are not infectious, we added a state variable,  $L$ , in a second model to represent the number of animals in a latent phase:

$$\begin{aligned} \frac{dS}{dt} &= a - S(\beta I + m) \\ \frac{dL}{dt} &= \beta SI - L\left(\frac{\mu}{\alpha} + m\right) \\ \frac{dI}{dt} &= \frac{\mu L}{\alpha} - I\left(\frac{\mu}{1 - \alpha} + m\right) \end{aligned}$$

where  $\alpha$  is a proportionality constant, in this context the proportion of the clinical course spent in latency.

Observations of the protracted time interval between infection and onset of clinical disease (Williams et al. 2002) suggest that there may be an incubation period in which the animal is infectious but does not suffer from increased disease-associated mortality. This hypothesis is represented by the following model:

$$\begin{aligned} \frac{dS}{dt} &= a - S[\beta(I + I_0) + m] \\ \frac{dI_0}{dt} &= \beta S(I + I_0) - I_0\left(\frac{\mu}{\alpha} + m\right) \\ \frac{dI}{dt} &= \frac{\mu I_0}{\alpha} - I\left(\frac{\mu}{1 - \alpha} + m\right) \end{aligned}$$

where  $I_0$  are incubating animals and  $\alpha$  is the proportion of the time interval between infection and death when animals are infectious but have the same mortality rate as susceptible animals.

There is experimental evidence that CWD may be transmitted to susceptible animals from excreta left in the environment by infected animals (Miller et al. 2004). To represent this hypothesis, we modeled indirect transmission as follows:

$$\begin{aligned} \frac{dS}{dt} &= a - S(\gamma E + m) \\ \frac{dI}{dt} &= \gamma SE - I(m + \mu) \end{aligned}$$

$$\frac{dE}{dt} = \varepsilon I - \tau E$$

where  $E$  is the mass of infectious material in the environment,  $\gamma$  is the indirect transmission coefficient [units = 1/(mass × time)],  $\varepsilon$  is the per capita rate of excretion of infectious material by infected animals, and  $\tau$  is the mass-specific rate of loss of infectious material from the environment. This model is based on two assumptions, that the instantaneous per capita rate of infection was directly proportionate to the mass of infectious material in the environment, i.e.,  $(1/S)(dI/dt) = \gamma E$ , and that the rate of uptake of infectious material by deer had negligible effects on the pool size. If we had been willing to assume that the dynamics within the environmental pool were much faster than dynamics of the susceptible and infected pools, then we could have constructed a more parsimonious two-compartment model that included an environmental source of infectivity (analogous to a free-living state) assuming  $E$  had reached equilibrium. Given the uncertainty in such an assumption and empirical evidence that the CWD agent can persist in the environment (Miller et al. 2004), we chose to explicitly model the environmental reservoir in our models.

In our models, indirect transmission is a function of area encountered by susceptible animals and infectious contacts with agent deposited in the environment, expressed as  $\gamma = (vA_S/A)$ , where  $A_S$  is the average area of the environment encountered by a susceptible animal per unit time,  $A$  is the total area used by the population, and  $v$  is the number of new infections produced per unit of mass of infectious material. Similar area-dependent arguments apply to the direct-transmission model.

Indirect transmission also was represented in a model that included additive effects of direct transmission between individuals,

$$\begin{aligned} \frac{dS}{dt} &= a - S(\beta I + \gamma E + m) \\ \frac{dI}{dt} &= S(\beta I + \gamma E) - I(m + \mu) \\ \frac{dE}{dt} &= \varepsilon I - \tau E \end{aligned}$$

and in a model that included a latent phase,

$$\begin{aligned} \frac{dS}{dt} &= a - S(\gamma E + m) \\ \frac{dL}{dt} &= S\gamma E - L\left(\frac{\mu}{\alpha} + m\right) \\ \frac{dI}{dt} &= \frac{\mu L}{\alpha} - I\left(\frac{\mu}{1 - \alpha} + m\right) \\ \frac{dE}{dt} &= \varepsilon I - \tau E. \end{aligned}$$

Each of these models makes explicit predictions about the total number of deaths from CWD ( $C$ ) that accumulate over time, using the following:

$$\frac{dC}{dt} = \mu I \quad \text{or} \quad \frac{dC}{dt} = \frac{\mu I}{1 - \alpha}$$

To evaluate support in the data for each model, we used observations of cumulative mortality from two distinct CWD epidemics in captive mule deer held at the Colorado Division of Wildlife (CDOW) Foothills Wildlife Research Facility (FWRP; near Fort Collins, Colorado, USA). CWD has occurred on the premises of what is now FWRP since at least the late 1960s (Williams and Young 1980). The first epidemic occurred during 1974–1985. After attempting to eradicate CWD from the FWRP in 1985, another epidemic (Miller and Williams 2003) (1992–2001) arose in a new deer herd assembled in 1990–1991. CWD deaths were diagnosed by recognition of a characteristic “wasting” syndrome (Williams and Young 1980) in affected animals prior to November 1978, by histopathology (Williams and Young 1980) from 1978–1996, and by histopathology or immunohistochemistry (Miller and Williams 2002) after 1996.

Because all models predicted CWD mortality, we were able to use observations on cumulative mortality during two epidemics to evaluate support in data for each model. Total additions to the population ( $a$ ) and per capita losses to natural deaths and removals ( $m$ ) were recorded annually. We used maximum-likelihood techniques to estimate initial conditions, transmission coefficients ( $\beta$ ,  $\gamma$ ), the proportion ( $\alpha$ ) of the clinical course in latency or incubation, the CWD mortality rate ( $\mu$ ), and rates of addition and loss of infectious residue ( $\epsilon$  and  $\tau$ , respectively). We estimated one initial condition for each model (the number of infected animals or the mass of infectious residue) at the beginning of each epidemic. The initial number of susceptible animals was the difference between known population size and estimated number of infected animals, and all other state variables were assumed to equal 0. Models were allowed to update all state variables during time 0 to time 1 and predictions of mortality were initiated at time 2.

We calculated the log likelihood ( $\ln \mathcal{L}$ ) of the  $i$ th year’s prediction of cumulative mortality by the  $j$ th candidate model conditional on the  $i$ th observation of mortality ( $x_i$ ) and the vector of parameters in the  $j$ th candidate model ( $\theta_j$ ):

$$\ln[\mathcal{L}(y_i|x_i, \theta_j)] = \ln\left\{\frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2}\left(\frac{y_i - x_i}{\sigma_{\text{obs}}}\right)^2\right]\right\}$$

where  $\sigma$  is the standard deviation calculated from the differences between model predictions and observations of cumulative mortality. The log likelihood of model  $j$  was then estimated as the sum of the log likelihoods across all observations.

In addition, we incorporated prior information on the rate of CWD mortality in our estimates of the likelihood of a model. Measurements of the duration of the clinical course in eight mule deer challenged orally with infectious brain tissue (E. S. Williams, *personal commu-*

*nication*) allowed us to estimate the mean and standard deviation of  $\mu$  (mean = 0.51; SD = 0.06). We calculated a likelihood of the difference between the maximum-likelihood estimate of the parameter of the CWD mortality rate ( $\mu_{\text{MLE}}$ ) and the empirically observed estimate ( $\mu_{\text{obs}}$ ) using

$$\ln[\mathcal{L}(\mu_{\text{MLE}}|\mu_{\text{obs}})] = \ln\left\{\frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2}\left(\frac{\mu_{\text{MLE}} - \mu_{\text{obs}}}{\sigma}\right)^2\right]\right\}$$

The total likelihood of the  $j$ th model given the data was then calculated as

$$\sum_{i=1}^n \ln[\mathcal{L}(y_i|x_i, \theta_j)] + \ln[\mathcal{L}(\mu_{\text{MLE}}|\mu_{\text{obs}})]$$

We integrated each model numerically using fourth-order Runge-Kutta. Maximum-likelihood estimates of model parameters and initial conditions were obtained using a trajectory-matching approach. Trajectory matching was chosen because we did not have observations of all state variables at all time steps. Maximum log likelihoods were estimated using a numerical search based on a generalized reduced-gradient algorithm (Lasdon et al. 1978). Convergence to a global maximum was assured by a multi-start search of the parameter space. We used Akaike’s information criterion ( $\text{AIC}_c$ ) for small samples and Akaike weights ( $w_i$ ; Burnham and Anderson 2002) to evaluate strength of evidence in data for competing models.

In addition to comparing alternative transmission models, we obtained model averaged estimates and associated confidence intervals on the basic reproductive number ( $R_0$ ) for models with Akaike weights  $\geq 0.05$ . Symbolic expressions for  $R_0$  were derived for each model, and model selection uncertainty and parameter uncertainty were calculated for numerical estimates of  $R_0$  by bootstrapping (Burnham and Anderson 2002:166). Five-thousand bootstrapped data sets were created for each model by randomly sampling model residuals (with replacement) and adding those residuals to the maximum-likelihood predictions of cumulative mortality. Competing models were fit to each bootstrapped data set. Maximum-likelihood estimates of model parameters of the model with the lowest  $\text{AIC}_c$  were used to calculate  $R_0$  using the appropriate symbolic expression, providing 5000 estimates of  $R_0$ . We calculated 95% confidence intervals on  $R_0$  as the upper and lower 0.025% percentiles of these estimates.

## RESULTS

The assumption of normally distributed, independent errors was supported by the data. Q–Q (quantile–quantile) scatterplots (Pawitan 2002:91–92) revealed linear trends between theoretical quantiles and sample quantiles and the Shapiro-Wilk test of normality did not allow rejection of the hypothesis of normally distributed errors ( $P$  ranged from 0.29 to 0.51 across models). There was no significant autocorrelation in errors for lags one or two in all models and only weak autocorrelation for

TABLE 1. Selection statistics for models representing competing hypotheses on routes of transmission of chronic wasting disease in mule deer based on a time series of 20 observations of annual disease mortality.

Model	$K^\dagger$	Log likelihood	$AIC_c^\ddagger$	$\Delta_r^\S$	$\mathcal{L}(\text{model}   \text{data})^\parallel$	$w_r^\P$
Indirect	7	-30.61	84.5	0	1.0000	0.57
Direct	5	-36.31	86.9	2.4	0.3065	0.17
Indirect with latency	8	-28.94	87.0	2.4	0.2976	0.17
Indirect + Direct	8	-30.17	89.4	4.9	0.0873	0.05
Direct with latency	6	-35.87	90.4	5.8	0.0548	0.03
Direct with incubation	6	-36.68	91.9	7.3	0.0259	0.01

$^\dagger$  The number of parameters and initial conditions estimated from the data, including the standard deviation.

$^\ddagger$  The Akaike information criterion corrected for small samples.

$^\S$  The difference in  $AIC_c$  for model  $r$  and the best model.

$^\parallel$  The likelihood of the model conditional on the data.

$^\P$  The Akaike weight.

lag three in two out of the five models. There were no discernable trends in the relationship between the magnitude of model predictions and the magnitude of residuals, or between the magnitude of the residuals and time.

A model of indirect transmission best represented the data (Akaike weight,  $w_r = 0.57$ ) (Table 1, Fig. 1). Two of the top three models contained terms for indirect transmission. Likelihood ratios (adjusted for difference in model parameters) revealed 3.8 times more support in the data for models that included indirect transmission as compared to models that represented direct transmission alone.

Model-averaged estimates of  $R_0$  (the basic reproductive number) were  $0.051S$  (95% CI =  $0.047S$ – $0.061S$ ). Based on initial population sizes in the two epidemics modeled, the value of  $R_0$  was 1.3 (95% CI = 1.1–1.6) for the 1974–1984 epidemic that was ongoing in 1974 and 1.5 (95% CI = 1.4–1.9) for the 1992–2001 epidemic that began in 1992.

#### DISCUSSION

Our findings add to accumulating evidence implicating transmission of chronic wasting disease (CWD) infection

through environmental pathways. In particular, our results are consistent with independent experimental findings that the CWD agent can be transmitted from residual excreta and carcass remains (Miller et al. 2004). Because all models were fit to the same data and because no experimental manipulation was involved, we cannot interpret these results as conclusive evidence of indirect transmission. Thus, although we cannot rule out direct contact as a pathway for transmission, the data at hand and the models considered provided more support for the environmental route. Moreover, the formulation of the indirect-transmission model does not rule out transmission as a result of exchange of infectious material between individuals—part of the reservoir of infectious material (i.e.,  $E$ ) could be found on animals. However, the environmental model is distinct from the direct-transmission model in representing the assumption that infectious material is durable and does not *require* contact with or the immediate presence of infected deer to perpetuate epidemics. We found limited support in the data for latency, consistent with observations that early accumulation of abnormal prion protein in gut-associated lymphoid tissue may equate to early onset of agent shedding (Hagenaars et al. 2003, Miller and Wild 2004).

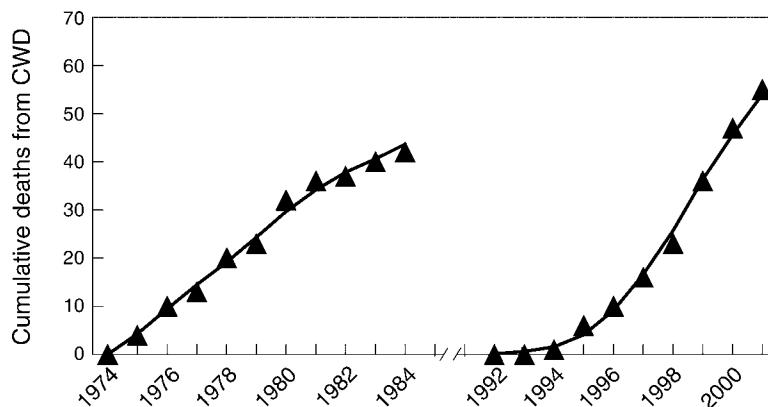


FIG. 1. Fit of the best approximating model to data from two epidemics of chronic wasting disease (CWD) in captive mule deer. The model represents indirect transmission of infectious agent from the environment to susceptible animals.

TABLE 2. Maximum-likelihood estimates and profile confidence intervals (in parentheses) for models with Akaike weights &gt; 0.05.

Model	Parameter					
	CWD mortality rate, $\mu$ (yr <sup>-1</sup> )	Direct transmission rate, $\beta$ (yr <sup>-1</sup> )	Proportion of clinical course in latency, $\alpha$	Indirect transmission rate, $\gamma$ (mass <sup>-1</sup> yr <sup>-1</sup> )	Rate of loss of infectious agent, $\tau$ (yr <sup>-1</sup> )	Per capita rate of excretion of infectious agent, $\epsilon$ (yr <sup>-1</sup> )
Indirect	0.567 (0.369–0.641)			0.787 (0.777–0.799)	2.55 (2.51–2.59)	0.111 (0.109–0.113)
Indirect + latency	0.546 (0.515–0.578)		0.486 (0.478–0.495)	1.13 (1.11–1.15)	5.66 (5.58–5.76)	0.332 (0.326–0.337)
Direct	0.481 (0.369–0.546)	0.0326 (0.032–0.034)				

Knowledge about the approximate value of  $R_0$  (the basic reproductive number) or the reproductive number ( $R$ ) of a pathogen is useful for designing control strategies (Diekmann et al. 1990). When the model representing disease dynamics is known with certainty,  $R_0$  or  $R$  can be calculated from estimates of model parameters incorporating uncertainty in parameter estimates alone. In diseases like CWD where mechanisms of transmission are poorly understood, however, there is also uncertainty in selecting the appropriate model. As a result, estimates of  $R_0$  must also reflect uncertainty in model selection. The model-averaged values of  $R_0$  estimated here are consistent with the tendency for CWD epidemics to be self-sustaining over time, but are lower than the value (3.9) calculated for scrapie in a flock of Cheviot sheep (Matthews et al. 1999).

Given that individual mule deer are not distributed randomly in space, but instead exist in aggregated social groups within populations, it is reasonable to expect that transmission processes, and thus  $R_0$ , are scale dependent. Consequently, our estimates can be scaled to reflect conditions for natural populations using the ratio of area used by an individual deer to the area used by a population, i.e.,  $A_S/A$ . Winter ranges of individual female mule deer in north-central Colorado (USA) average about 10 km<sup>2</sup> and ranges of wintering population units average about 100 km<sup>2</sup> (Conner and Miller 2004), so at these scales  $A_S/A \approx 0.1$ . Assuming that under conditions of confinement  $A_S/A \approx 1$ , we adjusted estimates of  $\gamma$  (the indirect-transmission coefficient) and  $\beta$  (the CWD-transmission coefficient) downward by an order of magnitude to approximate conditions experienced in free-ranging populations based on a 10:1 ratio of observed herd vs. individual winter range sizes (Conner and Miller 2004). We presumed that densities experienced at the scale of social groups resembled those seen in confinement and did not adjust estimates for these scales. Because the assumption of density-dependent CWD transmission may not faithfully represent contact structures in natural populations across all geographic scales, and because wintering mule deer groups appear to be an appropriate social unit for assessing epidemic dynamics of CWD (Conner and Miller 2004, Miller and Conner 2005), we did not attempt to extrapolate beyond this scale. Using scaled

estimates of  $\gamma$  and  $\beta$  and the other unscaled parameter estimates in Table 2, and assuming a natural mortality rate of 0.15 (Unsworth et al. 1999), the estimated model-averaged  $R_0$  was 0.00498 $S$  ( $S$  is the number of susceptible animals) for wintering mule deer population units. Winter ranges in north-central Colorado typically carry 400–1000 adult deer, and the corresponding estimated  $R_0$  values of 2–5 are consistent with the notion that long-term persistence of CWD in these population is likely (Gross and Miller 2001, Miller et al. 2000). Values of  $R_0 \approx 0.005S$  also suggest that CWD epidemics might not be sustained in areas where fewer than 200 individuals comprise a wintering group.

Indirect transmission by environmental contamination may complicate control efforts for CWD and other prion diseases. Control strategies have focused on reducing or eliminating CWD by culling or harvesting to increase the natural mortality rate in infected deer populations (Williams et al. 2002). The threshold natural mortality necessary to eradicate a disease is the value of  $m$  (the per capita mortality rate) necessary for  $R_0 < 1$ . For the direct-transmission model this value is  $m > \beta S - \mu$  ( $\mu$  is the per capita CWD mortality rate); for the indirect model the value is  $m > (\gamma\epsilon/S/\tau) - \mu$  ( $\gamma$  is the indirect-transmission coefficient,  $\epsilon$  is the per capita rate of excretion of the infectious agent, and  $\tau$  is the rate of loss of infectious material from the environment). It follows that the threshold for eradicating indirectly transmitted CWD will exceed the threshold for directly transmitted CWD whenever  $\gamma\epsilon/\tau > \beta$ . Our data do not allow us to distinguish estimates of the value of  $\beta$  from the value of  $\gamma\epsilon/\tau$ . However, we can conclude analytically that long persistence times (slow decay, small  $\tau$ ) or high excretion rates of infectious agent will make it more difficult to reduce or eradicate CWD as compared to the case of direct transmission. Better understanding of agent excretion and persistence are thus needed in order to make realistic assessments of the viability of specific CWD control strategies. Even under the most optimistic scenarios, however, it appears that extreme measures will be necessary to eliminate CWD from natural populations of deer once the disease becomes established. Using model-averaged parameter estimates and the foregoing scaling assumptions, the instantaneous rate of competing mortality necessary to drop  $R_0$  below

1 would exceed  $0.8 \text{ yr}^{-1}$ , implying that about 45% of the population would need to die annually from non-disease causes for a sustained period of time to effect control. The ecological and economic consequences of such interventions, as well as the relative merits of preventive management and of less severe interventions aimed at minimizing but not necessarily eliminating CWD, deserve careful consideration in the course of crafting long-term control strategies.

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