Pathogen-mediated selection and management implications for white-tailed deer exposed to chronic wasting disease

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Abstract

1. Pathogens can cause host extinction, affect population dynamics, and influence natural selection. Host susceptibility to pathogens can vary by species, demographics, and genetics which affect epizootic and population dynamics; ultimately determining population trends and evolution.
2. Chronic wasting disease (CWD), a fatal neuro-degenerative prion disease of cervids, has varying host susceptibility conferred by polymorphisms of the prion protein gene (PRNP) at codon 96 for white-tailed deer (*Odocoileus virginianus*). Deer with the homozygous Glycine allele (96GG) are most susceptible and a single Serine allele (96GS/96SS) reduces the risk of infection and mortality.
3. We developed epizootiological models that demonstrate CWD infection and disease-associated mortality were higher for the more susceptible (96GG) genotype; and, infection was higher for males than females. We used population models to evaluate future shifts in genotype frequencies under alternative harvest and infection rate scenarios.
4. Genetic shifts towards less susceptible genotypes were predicted as CWD prevalence increased during the course of an outbreak. This further increased CWD prevalence, and likely environmental contamination from prion shedding, due to longer incubation periods. Alternative harvest management strategies directly influenced CWD prevalence and spread, the rate of genetic selection, and deer population growth.
5. *Synthesis and applications*: We show that chronic wasting disease (CWD) transmission varied by sex, age class, and PRNP genotype, and that CWD disease-associated mortality varied by genotype. Together, these forces lead to CWD-mediated genetic selection for a white-tailed deer population. We predict that genetic selection pressure increases when hunter harvest pressure is lowered, and conversely, increasing hunter harvest can reduce genetic selection rates of antlered deer. Our results support the control of CWD prevalence by aggressive harvest of adult males, because they have the highest infection

rates. Our results have strong implications for evolution, disease ecology, geographic spread, disease mitigation, and cervid population management.

Key words: Infectious Disease Transmission, Disease Associated Mortality, Force of infection, Epizootic, Hunter harvest management, PRNP Genotype, Matrix population model, Wildlife disease

Introduction

Existing and emerging pathogens can drive population dynamics (Anderson & May, 1978; Daszak *et al.*, 2000), determine host geographic distributions (LaPointe *et al.*, 2012; Chafin *et al.*, 2020), and potentially drive host natural selection (LaCava *et al.*, 2021; Monello *et al.*, 2017; Goldmann, 2008; Van Blerkom, 2003). It is often difficult to identify which host genetic components are directly impacted by pathogen selection and to quantify the potential rate of population adaptation to pathogen pressures (Dwyer *et al.*, 1990; McKnight *et al.*, 2017). However, increasing application of genomic technology has enhanced research on pathogen driven selection (Blanchong *et al.*, 2016; Cornetti & Tschirren, 2020; Haworth *et al.*, 2021). Moreover, epizootilogical characteristics such as transmission dynamics, disease-associated mortality, and rate of spread can influence the selective forces acting upon free-ranging populations (Altizer *et al.*, 2003a). Heterogeneous transmission dynamics resulting from differences in social behavior, contact rates, and host demographics (Altizer *et al.*, 2003b; Cross *et al.*, 2009; Grear *et al.*, 2010) makes it complicated to understand the interacting factors that drive epizootics and affect host genetic selection (Dobson, 2004; VanderWaal *et al.*, 2014; Kardos & Shafer, 2018). As a result, few studies have measured the strength of selection pressure and rates of host genetic evolution in wildlife populations (Altizer *et al.*, 2003b; Robinson *et al.*, 2012a; Haworth *et al.*, 2021).

Investigations of disease dynamics in free-ranging animals often use disease prevalence, incidence, or antibody prevalence to measure disease frequency and estimate temporal and spatial disease dynamics. Alternatively, cross-sectional age-prevalence data are increasingly used to esti-

mate disease parameters for free-ranging animals (Heisey *et al.*, 2006, 2010; Samuel *et al.*, 2015; Samuel & Storm, 2016). However, potential biases arise for wildlife populations because ages of individuals are uncertain (Conn & Diefenbach, 2007; Storm *et al.*, 2014; Ketz *et al.*, 2019a). Methods to account for age misclassification must be considered to avoid spurious inference on force of infection and disease-associated mortality (Samuel & Storm, 2016). Force of infection, λ, is a key epizootiological parameter which measures the rate an uninfected individual will contract a disease and represents the foothold of a disease in a population (Heisey *et al.*, 2006; Farrington *et al.*, 2001). To assess the population impacts of a disease, it is also necessary to consider the increase in mortality hazard for a test-positive individual relative to a test-negative individual, defined as disease-associated mortality μ (Heisey *et al.*, 2006). When these disease parameters differ between polymorphic genotypes there is the potential for disease-driven genetic selection (Monello *et al.*, 2017). However, there has been limited evidence linking natural selection in wildlife populations with genetic heterogeneities in transmission or disease-associated mortality (Robinson *et al.*, 2012a). Heterogeneities inherent in the disease transmission or mortality processes also arise from differences in age, sex, behavior, and other host demographics, further complicating this assessment. Cervids are one of the most extensively managed groups in North America and world wide. In most areas, harvest represents the largest source of mortality, but the impact of harvest strategies on genetic selection is largely unknown.

Chronic wasting disease (CWD) is a neuro-degenerative disease of deer, elk, moose,and reindeer (cervids) caused by misfolded prion proteins (PrP^{CWD}). When mis-folded prion proteins are ingested, they can bind to normal prion (PrP^{C}), converting PrP^{C} into the pathogenic form (PrP^{CWD}). Over time, chronic wasting disease prions become widely distributed in nervous, lymphatic, blood, and muscle tissues in infected cervids and are shed via urine, feces, and saliva shortly after infection (Plummer *et al.*, 2017). As a result, CWD can be transmitted by direct (animal-to-animal) and indirect (environmental) routes during an extended incubation period. Currently, the relative importance of direct and environmental transmission during CWD epizootics is not currently understood (Ketz *et al.*, 2019a). The relatively slow accumulation of misfolded CWD prion proteins

in lymphoid and nervous systems leads to a prolonged incubation period of 2+ years, followed by behavioral signs of infection and ultimately death (Williams & Young, 1980). Vertical transmission is unknown in North American cervids, so new born animals are uninfected. Given the prolonged incubation period, young (< 2 years old) animals can become infected, but are unlikely to die from CWD (Samuel & Storm, 2016). Due to the prolonged incubation period and generally low rates of infection, deer typically show increased prevalence of infection with age, and infection is higher in males than females (Ketz *et al.*, 2019a). Species-specific polymorphisms in the prion protein gene (PRNP) confer varying host susceptibility to CWD, but none of the PRNP genotypes are immune to infection (Johnson *et al.*, 2006; Blanchong *et al.*, 2009; Robinson *et al.*, 2012c). Four PRNP genotypes (codons 95, 96, 116, and 226) are recognized as potentially important in determining CWD tolerance in white-tailed deer, but codon 96 appears to be the most important (Robinson *et al.*, 2012c; Haley *et al.*, 2019; Chafin *et al.*, 2020). Individuals with one copy of the Serine allele at codon 96 have lower infection rates, prolonged deposition of PrP^{CWD} prions in neurological tissues, and a prolonged pre-clinical phase (Johnson *et al.*, 2006, 2011; O'Rourke *et al.*, 2004, 2007; Robinson *et al.*, 2012a). Homozygotes with two copies of the Serine allele have lowest infection rates, but are uncommon in free-ranging populations (Robinson *et al.*, 2012c; Haley *et al.*, 2019). For example, the frequency of homozygous least susceptible white-tailed deer (*Odocoileus virginianus*; WTD) was less than 2% of the population in Wisconsin (Robinson *et al.*, 2012c), whereas heterozyotes were ~26%. The low frequency of these less susceptible genotypes suggests that non-random mating or differential genetic fitness may occur (Robinson *et al.*, 2012c,b; Wolfe *et al.*, 2012).

Genotype-specific infection or disease-associated mortality rates implies that evolution can occur through changes in allele frequency due to pathogen-driven selection. Models suggest this selection pressure could act on a time scale of decades and that less susceptible alleles may become dominant in the future (Robinson *et al.*, 2012a; Williams *et al.*, 2014). For example, Monello *et al.* (2017) found that elk populations with a long history of CWD exposure had higher frequencies of less susceptible alleles compared to populations with limited CWD exposure. LaCava *et al.*

(2021) found that less susceptible mule deer (*Odocoileus hemionus*) were less likely to be positive for CWD and the less susceptible allele was more common in populations exposed to CWD for longer. However, emerging strains of infectious PrP^{CWD} suggest that both transmission dynamics and clinical signs may be altered in the future (Herbst *et al.*, 2017). Ultimately, fitness differences that arise from differential infection and survival are critical to determine the population impacts and long term transmission dynamics of CWD.

Few wildlife studies have examined the link between host demographics, genetic susceptibility, rate of pathogen infection, disease-associated mortality, and hunter harvest because these processes are studied at scales that vary from an individual level to broad population and ecological scales (Zipkin *et al.*, 2021). However, these factors are all critical mediators of population dynamics and can lead to disease driven selection. Previous CWD studies in Wisconsin demonstrated genetic differences in infection and survival for adult female deer (Robinson *et al.*, 2012a), or sex and age differences in force of infection and disease-associated mortality (Samuel & Storm, 2016). However, it is unknown whether CWD driven genetic selection differs for male and female deer. Furthermore, hunter harvest has been the primary source of mortality and the primary management tool for controlling white-tailed deer populations (Brown *et al.*, 2000; Woolf & Roseberry, 1998). Disease-driven genetic selection is also affected by competing sources of mortality, including hunter harvest, predation, natural mortality, and disease-associated mortality. We assess how heterogeneous infection and harvest mortality designed to manage deer populations can affect selection pressure and shape the future genetic composition and abundance of wildlife populations.

The goal of our study was to examine CWD infection and mortality patterns using age-corrected cross sectional data from harvested deer coupled with PRNP sequencing of codon 96, which is the main allele associated with CWD susceptibility for white-tailed deer (Haley *et al.*, 2019; Chafin *et al.*, 2020). We used data on sex, age class, and CWD status from over 13000 harvested deer. We corrected for age class misclassification and imputed PRNP genotype frequencies based on a sub-sample of over 2200 harvested deer. We used the resulting frequency distributions from the sex, corrected age class, CWD status, and imputed genotype (48 groups of deer) to account for het-

erogeneity in key epidemiological parameters, including force of infection and disease-associated mortality. We used deterministic population simulations to evaluate potential changes in future genotype frequencies under different hunter harvest and CWD infection rate scenarios. We show that pathogen-mediated selection is occurring in white-tailed deer populations affected by CWD due to differential force of infection and disease-associated mortality. These findings have direct implications for harvest management strategies, disease ecology, evolution, geographic spread, disease mitigation, and cervid population management.

Materials and Methods

Study Area and Surveillance Data

Samples from 1154 male and 1108 female deer were obtained from the CWD "core area" of south-central Wisconsin, the region where CWD was first detected in the state (see Fig. 1 in Samuel and Storm, 2016). The core area is comprised of 210 sections (544 km^2) of continuous deer habitat, containing the highest (6.2 percent) and uniform spatial prevalence of CWD post discovery (Joly *et al.*, 2006). Samples were primarily from hunter harvested deer, during the early phase of the epizootic from 2002-2010. Grear *et al.* (2006) found no difference in hunter harvest rates for CWD infected versus uninfected deer. Mandatory registration and CWD testing facilitated the collection of sex and age class data for each deer. Age classes were determined by Wisconsin Department of Natural Resources (WDNR) personnel using tooth replacement and wear criteria. Retropharyngeal and obex tissues for CWD testing and genetic analysis were collected by WDNR staff from deer during registration. CWD positive status was determined by the Wisconsin Veterinary Diagnostic Laboratory based on immunohistochemistry or plate ELISA for either tissue (Keane *et al.*, 2008).

PRNP Genotyping

PRNP genotypes for deer were determined by three methods. Robinson *et al.* (2012a) determined PRNP genotypes (96GG and 96GS/SS) for deer using a single nucleotide polymorphism (SNP) assay targeting codon 96. Briefly, whole genomic DNA was extracted from lymph node tissue

using the Qiagen DNeasytissue extraction kit (Qiagen Ltd., Crawley, West Sussex, UK). SNP assays were run at the University of Wisconsin, Madison Biotechnology Center (UWBC) using nested primers (See Table S2 and Robinson *et al.* (2012a) for details). Genotypes were read on a Biotek Synergy II plate reader (Biotek, Winooska, VT) and scored using the RGUI Statistical Computing package (R Core Team, 2019). An additional group of harvested deer were genotyped by Johnson *et al.* (2006) from ear or muscle tissue using the DNA IQ System (Promega, Madison, Wisconsin) and the coding region of the PRNP gene was amplified and sequenced as described previously (Johnson *et al.*, 2003) (Table S2). In addition, we extracted DNA from ear tissue of four older female deer with the Qiagen Genomic-tip Extraction Kit. PCR and Sanger sequencing were performed at the UWBC as in Table S2 following protocols described in Johnson *et al.* (2006). Samples were electrophoresed on an Applied Biosystems 3730xl automated DNA sequencing instrument. Data were analyzed using Sequencing Analysis v6 and GeneStudio v2.2.

Statistical Analysis

Most infected individuals (626 of 853) from the core area were genotyped. An age-stratified random sub-sample of CWD negative deer were also genotyped, except that most individuals of the oldest age classes were also genetically tested. In total, 17.3% of the deer (> 1 year old) tested for CWD (n=13093) were also genotyped (n=2262) during the study period. We used Bayesian methods (Ma & Chen, 2018) to impute genotype frequencies for harvested deer where this information was missing and thereby make improved inferences to the "population" of harvested deer (Sterba, 2009; Kim *et al.*, 2017). The Bayesian approach provides a natural way to take the uncertainty from missing data into account when making inferences on incomplete data (Daniels & Hogan, 2008; Ibrahim *et al.*, 2005). We developed alternative models to predict the missing PRNP genotype frequencies (by age, sex, and CWD status groups) of harvested deer that were not genetically tested. When missing values can be modeled from the observed data, imputation models can be used to provide both improved and less biased estimates of the missing observations for statistical inference. For the genotyped deer, we used Bayesian logistic regression with uninformative

priors on the coefficients to predict genotype based on sex, age class, and CWD infection status. We selected the best predictive model using the minimum Watanabe Akaike Information Criterion (WAIC) (Watanabe, 2010) to impute the PRNP genotype frequencies for the entire population of harvested deer, while accounting for associated error distributions.

Epidemiological analyses of age-prevalence data assume that ages are determined without bias. However, Storm *et al.* (2014) showed that male and female age classes based on tooth wear are biased (mis-classified) compared to age classes based on cementum annuli and these biases lead to incorrect estimation of CWD prevalence, infection rate, and mortality (Storm *et al.*, 2014; Samuel & Storm, 2016). To correct the age misclassification resulting from using tooth wear for 6,495 female and 6,598 male harvested deer we used paired data for cementum annuli and tooth wear for 1,261 of these deer (see Storm *et al.* (2014) for details). Following Samuel & Storm (2016), we used a cumulative logit model (Liu & Agresti, 2005) to fit the ordinal age classification data and correct the age composition of harvested deer within all sex and genotype groups. We used the flexibility of the Bayesian approach to adjust the age-prevalence rates in a single model, propagating the uncertainty for each step of the analysis described above. Three chains of 500,000 Markov chain Monte Carlo (MCMC) iterations were generated using nimble (de Valpine *et al.*, 2017), with a burn-in of 250,000 iterations. Model diagnostics indicated convergence of the posterior distributions of all parameters using traceplots and Gelman-Rubin statistics (Gelman & Rubin, 1992). Thus, we obtained age adjusted posterior distributions of CWD prevalence ($\delta_{a,i,g}$) for each sex i ={female, male}, genotype g ={"96GG","96GS/SS" }, and age class $a = \{1.5, 2.5, 3.5, 4.5 - 5.5, 6.5 - 8.5, 9.5+\}$.

We fit four epizootiological age-prevalence models to the age-corrected and genotype predicted CWD prevalence rates for all four sex-genotype categories ($\delta_{i,g}$) using average age within each age class. We used a subset of the models from Samuel & Storm (2016) that accounts for differences in sex and age specific force of infection rates (λ) and disease-associated mortality (μ) (Storm *et al.*, 2013; Jennelle *et al.*, 2014). Force of infection is the exponential hazard rate at which test-negative individuals become test-positive (Heisey *et al.*, 2006, 2010). Disease-associated mortality is the

increase in exponential mortality hazard rate between infected and uninfected deer (Caley & Hone, 2002; Heisey *et al.*, 2006). First, we considered two simple models where force of infection and mortality parameters were equal for both yearlings (1.5 years old) and adults. We also considered two increasingly complex models where force of infection for yearlings differed from adults with no disease-associated mortality for yearlings because the prolonged clinical course of CWD is unlikely to lead to mortality for the yearling age class (Storm *et al.*, 2013; Samuel & Storm, 2016). One model restricted disease-associated mortality to be equal for both sexes ($\mu_{\text{male},g} = \mu_{\text{female},g}$) while the other allowed for sex-specific rates ($\mu_{\text{male},g} \neq \mu_{\text{female},g}$). All epizootological models were based on the formulation of Cohen (1973) without recovery because CWD is always fatal:

$$p_{i,g}(a) = \frac{\lambda_{i,g}(\exp\{-\lambda_{i,g}a\} - \exp\{-\mu_{i,g}a\})}{\mu_{i,g}\exp\{-\lambda_{i,g}a\} - \lambda_{i,g}\exp\{-\mu_{i,g}a\}}, \tag{1}$$

where $p_{i,g}(a)$ is the prevalence of the average age within age class a, sex i, and genotype g. The annual survival ratio ($\rho = \exp\{-\mu\}$) is the relative rate of annual survival for an individual that is alive and test-positive relative to one that remains negative (Heisey *et al.*, 2006). For ease of interpretation, we also calculated the annual infection probability from the force of infection hazard rate using $\psi_{i,g,a} = 1 - \exp(-\lambda_{i,g,a})$ for each of the age-sex-genotype groups.

We used a second Bayesian model to obtain posterior distributions for the parameters in equation 1. We used the mean of the posterior distributions of the observed and age adjusted population level prevalence rates for each group from the previous model, accounting for uncertainty using the standard deviations of the posteriors in the likelihood

$$\delta_{i,g} \sim \text{normal}(p_{i,g}, \sigma^2_{i,g}). \tag{2}$$

Samuel & Storm (2016) found that additional distributions did not improve model fit, so we adapted the same likelihood. We used 200,000 MCMC iterations following a burn-in of 100,000 iterations to obtain posterior distributions of the epizootiological parameters. We used informed beta prior distributions for the force of infection rates calculated using moment matching means

and approximate standard deviations based on confidence interval bounds from a transformation of the estimated annual incidence rates from Edmunds *et al.* (2016) (Supplement S1). We used informed gamma priors for the differences in disease-associated mortality parameters, allowing for different hyper-parameters calculated by moment matching a transformation of the ratio of survival rates of infected versus uninfected adult sex groups estimated using telemetry data from an ongoing study in the same region (*unpublished data*, Supplement S1). A sensitivity analysis indicated no influence of the prior distributions on the posteriors (Supplement S1). Model selection was based on the minimum WAIC values (Supplement Table S6). The ratio of posterior distributions of the annual infection probabilities of each of the genotype groups were calculated to determine the relative strength of effects.

Because the frequency of the 96SS genotype in deer populations is lower than would be expected by random mating (Robinson *et al.*, 2012c), it has been hypothesized that the 96SS genotype has lower fitness than the 96GG genotype in the absence of CWD, either due to lower survival and/or non-random mating. However, calculating different survival rates of genotypes from our cross-sectional data is not possible with the limited number of 96SS animals. To assess potential differences in survival of the two genotypes (96GG vs 96GS/SS) in the absence of CWD infection, we calculated a change-in-ratio posterior distribution for survival between subsequent age classes of uninfected deer, for the sexes combined, and for each sex separately (Paulik & Robson, 1969). The relative survival s of an individual of x type versus y type, from age a_1 to the subsequent age a_2, can be expressed as

$$\frac{s_x}{s_y} = \frac{\left(\frac{y_{a_1}}{x_{a_1}}\right)}{\left(\frac{y_{a_2}}{x_{a_2}}\right)}, \tag{3}$$

where x and y represents the respective number of uninfected individuals alive (harvested) at a given age a for the 96GS/SS and 96GG genotype groups. We hypothesized that the change-in-ratio would be less than 1, because 96GS/SS having lower relative survival of uninfected individuals could explain why their population frequency is lower than expected. We evaluated the change-in-ratio from CWD test-negative individuals only.

Predicting Genotypic Changes

We used sex-specific deterministic population simulations to evaluate potential changes in genotype frequencies over time under different hunter harvest and CWD infection rate scenarios. We used Leslie matrix models parameterized using sex-specific harvest, survival, and fecundity rates (Jennelle *et al.*, 2014). We used separate Leslie matrix models for males and females to account for differential breeding success for males due to age-dominant breeding and differential longevity of males based on PRNP genotype (See Supplement S3 for simulation details). Our models used two PRNP genotype groups (96GG and 96GS/96SS) because there is no current evidence of demographic differences between 96GS and 96SS deer. We used means of the posterior distributions of our modeling results to incorporate CWD and PRNP genotype-specific annual infection and disease-associated survival rates. Initial matrix values were obtained from the age-corrected and genotype extrapolated posterior distributions of the stable age distributions from the sex-genotype-age classes. We obtained initial age-specific population values within the genotype-sex-age classes by multiplying the posterior means for each age class by the normalized within age-class weights associated with stable age distributions from Osnas *et al.* (2009). We simulated the population trajectory for 100 years and annually calculated the relative frequency of 96GS/SS and 96GG genotypes, summing over the number of CWD-infected and uninfected individuals. We used Mendelian inheritance to determine the number of sex- and genotype-specific fawns (Appendix S3.3) at each time step to account for mixing of allele frequencies during breeding, because fawns inherit their genotype from both parents. We ran simulations with varying hunter harvest rates for antlered and antlerless deer. We restricted harvest rates (0.01, 0.11, 0.21, 0.31) to values where the growth rate for an uninfected population was >=1. To assess the effect of increased prevalence (and therefore infection rate), we ran simulations where force of infection rates were increased by 1, 5, 10 and 15 fold. Although infection rates have not been estimated for populations with CWD prevalence > 10 percent we found that a 15 fold increase produced prevalence values that were similar to those currently found in south-central Wisconsin and higher infection rates were found in areas

outside the core area of south-central Wisconsin (Jennelle et al., 2014). Previously, infection rates approximately 20 fold higher have been reported for captive deer (Keane et al., 2008).

Results

Genotype Sequences

Three of the four newly sequenced female deer had PRNP genotype 96GG and one was heterozygous for 96GS. Full sequences are available on GenBank (accession numbers). Across all 2262 sequenced deer in the study (SNP analysis, previous sequences, and newly sequenced individuals), the 96GG allele was the most common, with a frequency of 0.61, 96GS appeared at a frequency of 0.35, and 96SS was rare at a frequency of 0.04 (see Supplement Table S8 for a breakdown by sex, age class, PRNP genotype, and CWD status). All newly sequenced deer in this study exhibited the wildtype genotype at codons 116 and 226, which have been found to be variable in other populations (Haley *et al.*, 2019).

Modeling Results

The best predictive model for PRNP genotype included CWD infection status only (Supplement Table S6) based on WAIC. Two alternative models had < 2 ΔWAIC, suggesting that including sex or age class produced similar predictive capability. However, the 95% equal-tailed credible bounds of the posterior distributions of the coefficients overlapped 0, so we excluded them in the final model (Supplemental Table S7 and Figure S5).

Tooth replacement and wear underestimated the cementum annuli ages of older females, and overestimated the yearling age class. Males had inconsistent correction patterns for the age classes (Supplement Figure S6). Age-corrected prevalence for males was monotonically increasing for both genotypes, and for the 96GS/SS genotype for females. The oldest female 96GG age class had a slightly lower age-corrected prevalence than the prior age class (Figure 1). Corrected prevalence for males was nearly double females for all age classes ≥ 2 years old and for both genotypes, while the yearling prevalence for both genotypes was only slightly greater for males. Corrected

prevalence was about twice as high for 96GG compared to 96GS/SS genotypes.

[Figure 1 about here.]

[Table 1 about here.]

[Table 2 about here.]

[Figure 2 about here.]

We found that more complex epizootiology models had more support from the age and genotype corrected data (lower WAIC). The best model included different force of infection between genotypes (96GG denoted G, and 96GS/SS denoted S), yearlings and adults, and sex ($\lambda_{M\neq F\neq Y,G\neq S}$). Disease-associated mortality was equivalent across the sexes but differed between the genotypes ($\mu_{M=F,G\neq S}$) with no disease-associated mortality for yearlings $\mu_Y = 0$ (Table 1). Differences in annual probability of infection were substantial and credible bounds did not overlap between sexes, age groups (adult/yearling) or genotypes (Figure 2). Adult males with 96GG had annual infection probabilities of 0.25 (0.22,0.27) compared with 0.07 (0.06,0.08) for the 96GS/SS genotype. Adult females had annual infection probabilities of 0.11 (0.1,0.13) and 0.03 (0.02,0.03) for the 96GG and 96GS/SS genotypes, respectively. Overall, the ratio of annual infection probabilities showed that 96GG compared with 96GS/SS genotypes had annual infection probabilities that were 2.5-4 times higher for yearlings, 2.5-4.5 times higher for adult males, and 3-6 times higher for adult females (Figure 2).

Our top model showed disease-associated mortality was equivalent between sexes but with differences between the genotypes $\mu_{\mathrm{F=M},G\neq S}$. The 96GG genotype had higher disease-associated mortality (mean $\mu_{\mathrm{GG}} = 1.53$ BCI=(1.35,1.74)) than the 96GS/SS genotype (mean $\mu_{\mathrm{GS/SS}} = 1$, BCI=(0.79,1.25)), with a 1% overlap in posterior distributions. Correspondingly, posterior distributions of relative annual survival for CWD infected 96GG deer was lower with (mean $\rho_{\mathrm{GG}} = 0.22$, BCI=(0.18,0.26)) than the less susceptible genotype (mean $\rho_{\mathrm{GS/SS}} = 0.37$, BCI= (0.29,0.45)) (Figure 2).

Change-in-ratio relative survival rates for uninfected deer were similar between the genotypes when sexes were combined and also considered separately (Supplemental Figure S7) as all posteriors included 1 within the 95% credible bounds. The probability that relative survival was less than 1 was 0.71 for the sexes combined, 0.66 for females, and 0.77 for males, providing some support for our hypothesis that uninfected 96GS/SS deer have lower survival than uninfected 96GG deer.

[Figure 3 about here.]

[Figure 4 about here.]

Predicting Genotypic Changes

Genotype frequency projections showed several, sometimes competing, factors influence the potential selective pressure on PRNP genotypes. Disease-driven selection was evident, and the proportion of less-susceptible 96GS/SS genotypes increased over the span of 100 years (primarily during the first 50 years) under all simulation scenarios (Figures 3 and 4). As CWD epizootics continue, disease prevalence increases in the population, which also leads to higher force of infection (Jennelle *et al.*, 2014). Higher force of infection intensified the selective pressure favoring the less susceptible 96GS/SS genotype, which increased in frequency at a greater rate as force of infection increased (Figure 3). The frequency of females with PRNP genotypes 96GS/SS increased by 18% after 100 years under observed infection rates without harvest, but by 39% when force of infection was increased 15 fold. Similarly, the frequency of 96GS/SS males increased by 23% after 100 years under observed infection rates without harvest, and increased by 42% with the 15 fold increase in infection. Hence, disease driven selection roughly doubled with increasing infection rates for both sexes in the absence of hunter harvest.

In contrast, harvest reduced the effect of disease-driven selection pressure. All scenarios including harvest showed a dampening of the selective pressure favoring 96GS/SS, with increasing harvest rates having a greater effect on genotype frequencies than infection rates. Under observed infection rates, as harvest levels were shifted from 0.01 to 0.31, the frequency of 96GS/SS deer at

the end of the 100 year simulation were 9% lower for females, and 8-14% lower for males (depending on level of antlerless harvest impacting juvenile males; Figure 4). We also found that antlered harvest had no impact on female genotype selection (results not shown). In contrast, higher harvest rates of antlerless deer, which includes male fawns, lead to higher frequencies of the 96GS/SS male deer. These apparently contradictory results occur because the average age of the population of males increases due to the reduction in male fawns, coupled with higher survival and greater age-related breeding success of 96GS/SS males. Under observed infection rates, and antlerless harvest of 0.01 vs 0.31, the average age of 96GS/SS breeding males was 3.66 and 3.95, respectively; higher than 3.32 and 3.51 for 96GG males. Moreover, under moderate antlered harvest, the proportion of 96GS/SS male fawns produced under high antlerless harvest was 4% higher than under low antlerless harvest, indicative of increased breeding success of 96GS/SS males.

Discussion

Correct age classification of wildlife species is notoriously difficult (Conn & Diefenbach, 2007; Storm *et al.*, 2014; Ketz *et al.*, 2019a) and can affect epidemiological parameters (Lachish & Murray, 2018; Samuel & Storm, 2016; Storm *et al.*, 2014). Our model results for age correction was consistent with results from Samuel & Storm (2016). The pattern of age bias in adult females is consistent with known classification bias where adult females are over-placed in younger age classes (Ketz *et al.*, 2019a; Smith & McDonald, 2002). We also found that CWD status was the most important predictor of PRNP genotype for deer whose genotype was unknown (Supplemental Table S6 and Figure S5), and predictions were consistent with those from Robinson *et al.* (2012a). Prevalence rates of the age-corrected, PRNP genotype predicted distributions (Figure 1) showed monotonically increasing infection rates for all age classes of deer; a characteristic of chronic disease where cumulative risk increases with time of exposure. The one exception was the oldest (9+ age class) 96GG adult females, which had overlapping prevalence with the 6-8 year old age class. However, these prevalence rates for older age classes should be interpreted cautiously because of smaller sample sizes. We used the age-corrected, PRNP genotype predicted posterior distributions for over 13,000 deer harvested during the early phases of a prion outbreak to derive key

epizootiological parameters that provide insight into the role that CWD pathogens have in structuring populations (Anderson & May, 1978). Transmission dynamics such as the force of infection (Caley & Hone, 2002) and disease-associated mortality can inform us about the increased fitness costs associated with pathogens (Caley & Hone, 2002; Heisey *et al.*, 2006). We found that CWD has different effects on age, sex and PRNP genotype of white-tailed deer.

Although all PRNP genotypes are susceptible to CWD infection (Haley *et al.*, 2019), susceptibility and disease progression varies among species-specific genotypes (Robinson *et al.*, 2012c). Our results show that wild deer with the PRNP 96GG genotype are 3-4 times more likely to become infected with CWD than deer with the PRNP 96GS/SS genotypes. Annual CWD infection probabilities in adult (>1.5 years) males were more than twice those for adult females, for both genotypes (Table 2). Adult males with the PRNP 96GG genotype had the highest annual probability of infection of all cohorts, followed by the adult female 96GG genotype (Figure 2). Although CWD infection was much lower in the PRNP 96GS/SS genotypes, adult males had 2-3 times higher probability of infection than adult females. In addition, annual infection probability in yearlings was much lower than either adult females or males, but still higher for the yearlings with the 96GG genotype compared to 96GS/SS.

The reasons for these sex and age differences in infection are generally unknown, but likely provide important keys for CWD management in white-tailed deer, and also in mule deer, which have similar CWD prevalence patterns (Miller & Conner, 2005). O'Brien *et al.* (2002) observed similar sex-specific bovine tuberculosis infection patterns in Michigan white-tailed deer (a chronic bacterial infection), suggesting similar transmission routes for both diseases. It appears that adult females are primarily infected with CWD from contact with related females in their area or nearby (Grear *et al.*, 2010; Cullingham *et al.*, 2011). One study suggested yearlings may have less susceptibility to infection than adults due to differential development of Pyers patches which affect CWD prion uptake in the gut (Heisey & Joly, 2004). In contrast, it has been hypothesized that adult males might acquire CWD infection from females during mating, from environmental sources, or from social contact with other males in bachelor groups during the non-breeding season (Grear

et al., 2006; Samuel & Storm, 2016). The high rates of infection in adult male deer provides support for management strategies that reduce the number of older males to control CWD prevalence (Jennelle *et al.*, 2014; Miller & Fischer, 2016; Miller *et al.*, 2020; Conner *et al.*, 2021). Better understanding of these transmission routes and rates among free-ranging deer would contribute to the development of strategies to control CWD, especially strategies that reduce infection in males and subsequently lower population levels of infection via frequency-dependent transmission (Potapov *et al.*, 2012; Jennelle *et al.*, 2014; Samuel & Storm, 2016).

Once adult deer become infected with CWD, the likelihood of continued survival is substantially reduced compared to uninfected deer. This disease-associated mortality is higher for 96GG deer than for 96GS/SS deer. Annual probability of survival for infected adults was reduced by 0.78 and 0.63 compared to uninfected adults with 96GG and 96GS/SS genotypes, respectively. It is important to note these values represent additive mortality for infected deer, including harvest impacts. These results were the same for both female and male deer indicating that PRNP genotype was the most important driver of CWD-associated mortality. Variation in disease-associated mortality between genotypes likely occurs because deposition of CWD prions in the obex, which causes clinical disease, is prolonged for individuals with 96GS/SS genotypes (Johnson *et al.*, 2006, 2011; O'Rourke *et al.*, 2004, 2007; Robinson *et al.*, 2012c). Our mortality results differ from Samuel & Storm (2016) who reported higher mortality for males than for females but they did not consider PRNP genotype in their analysis. We believe the differences occur because 96GG males have the highest rate of annual infection combined with a high rate of mortality.

In the Wisconsin core area, Grear *et al.* (2006) and Heisey *et al.* (2010) found that CWD status did not influence hunting mortality, at least during the early phase of the epizootic. We are not aware of any study evaluating differential harvest of deer with different PRNP genotypes; however, a number of deer studies evaluating genotypic differences in CWD status have also assumed harvest was not based on PRNP genotype (see Robinson *et al.* (2012a); Ketz *et al.* (2019a)). PRNP genotype distributions have consistently demonstrated that the frequency of least susceptible PRNP alleles are uncommon (Robinson *et al.*, 2012c; Monello *et al.*, 2017; LaCava *et al.*, 2021). These

findings have led to the hypotheses that the low frequency of least susceptible PRNP genotypes is a result of non-random mating or reduced fitness in the absence of CWD (Robinson *et al.*, 2012c,a; Wolfe *et al.*, 2012). We compared relative survival of uninfected 96GG and 96GS/SS deer using a change-in-ratio from one age class to the subsequent age class with sexes combined or considered separately (Supplemental Figure S7). Our results indicated similar survival of the uninfected 96GG and 96GS/SS deer because the posterior distributions of the ratios all overlapped 1. Unfortunately, we were unable to directly compare 96GG with 96SS genotypes because there were too few deer with the 96SS allele. We suspect it will be difficult to evaluate differences in fitness of these genotypes until 96SS animals become more abundant.

We found that Wisconsin deer are likely experiencing genetic selection caused by CWD with potential long-term implications for disease dynamics and management (Robinson *et al.*, 2012a). In our simulations, increasing infection rates accelerated genotype selection and increased the final proportion of 96GS/SS genotypes by 0.20 (Figure 3). As the frequency of the 96GS/SS genotype increased we also found that population prevalence increased (Supplement C3 Table S5). Substantial shifts in genetic composition favoring the less susceptible 96GS/SS genotypes are expected, but these shifts could take decades. Several factors will likely affect the rate of genotypic shift (Figure 5). Increasing prevalence rates are a common pattern in CWD epizootics and drive higher infection rates via frequency dependent transmission (Jennelle *et al.*, 2014). These higher rates of infection produce higher selection pressure and increases the shift to less susceptible genotypes. The longer incubation period in 96GS/SS deer results in higher population prevalence because these infected deer live longer than 96GG deer (Robinson *et al.*, 2012a), indicating that shifts towards less susceptible genotypes are likely to exacerbate, rather than mitigate future prevalence. Moreover, this prolonged life span of infected 96GS/SS deer may increase transmission if these deer are shedding infectious prions for a longer duration (Robinson *et al.*, 2012a; Williams *et al.*, 2014; Plummer *et al.*, 2017). Because male deer have higher rates of infection than females, they will likely see earlier genotypic shifts and reach a higher proportion of 96GS/SS genotypes (Figure 3). Older dominant males, which are more likely to be a less susceptible genotype, are more likely

to successfully breed with females (DeYoung *et al.*, 2004; Sorin, 2004), potentially contributing to genotype selection. This topic merits further consideration.

[Figure 5 about here.]

In contrast to higher infection, harvest of deer populations will reduce selective pressures because deer are removed independently of their genotype (Figures 4 and 5). We found increases in antlerless harvest, which includes male fawns, had minimal effect on the rate of genotype selection and eventual frequency of less susceptible females, likely because females and young deer have the lowest infection rates. Increased harvest of antlered males substantially delayed the rate and final level of male genotype selection to 96GS/SS (Figures 4). Essentially, high antlered harvest rates can offset increased genetic selection resulting from higher infection. High antlered harvest is also expected to drive down prevalence rates of adult males thereby reducing CWD transmission in the population (Table S5). However, when both antlered and antlerless harvest occurred, we found that higher antlerless harvest increased the rate of conversion and final level of male 96GS/SS genotypes, because the reduction of male fawns causes an increased proportion of 96GS/SS males in older age classes, resulting in higher per capita breeding by the older, less susceptible 96GS/SS males compared to 96GG males. As a result, the proportion of the 96GS/SS male fawns also increases. Our simulations show that antlerless harvest levels currently used to control deer populations (0.31) can lead to population declines as CWD prevalence, and consequently, infection rates increase, which are characteristic of CWD epizootics (Supplemental Table S5). This means lower harvest rates will be required to maintain sustainable deer populations as CWD prevalence increases during the advanced stages of an outbreak. These results also support previous studies showing the negative impacts of CWD on cervid populations (Edmunds *et al.*, 2016; DeVivo *et al.*, 2017; Jennelle *et al.*, 2014; Monello *et al.*, 2014). An important limitation of our genetic selection simulation is that we were unable to specifically model the 96SS genotype because CWD infection and mortality parameters are unknown. We assumed that 96GS/SS genotypes were composed of approximately 15 percent 96SS deer, likely underestimating the eventual proportion of 96GS/SS genotypes in the population simulation.

In the absence of strategies to manage CWD epizootics, predictions indicate that disease prevalence and spread will likely increase (Robinson *et al.*, 2013; Almberg *et al.*, 2011; Jennelle *et al.*, 2014; Ketz *et al.*, 2019b). Increasing prevalence leads to higher mortality and cervid population declines (Edmunds *et al.*, 2016; DeVivo *et al.*, 2017; Monello *et al.*, 2014) which will require changes in harvest management to maintain sustainable populations (Williams *et al.*, 2014) (Figure 5). Declining population trends will be accompanied by shifts in PRNP frequency favoring less susceptible genotypes (Robinson *et al.*, 2012c; Williams *et al.*, 2014), which will likely increase future CWD prevalence. Higher prevalence will also increase the rate of disease spread via dispersal of more infected juvenile deer (Ketz *et al.*, 2019b). However, there are many uncertainties that could influence future CWD trajectories. First, longer survival of infected 96GS/SS genotypes can lead to higher prevalence rates, and could increase infection rates via direct contact or environmental routes depending on prion shedding patterns (Robinson *et al.*, 2012c; Samuel & Storm, 2016; Plummer *et al.*, 2017). Both direct and environmental transmission are likely to be additive forces of infection (Ketz *et al.*, 2019b), potentially contributing to increased persistence and increased virulence of the CWD agent (Brown & Gajdusek, 1991; Pedersen *et al.*, 2007; Johnson *et al.*, 2007). Second, less susceptible PRNP genotypes are typically uncommon in unaffected cervid populations. Thus, genetic shifts favoring less susceptible genotypes could lead to unexpected changes in deer demographics, particularly reduced survival and/or recruitment. Mead *et al.* (2003) found evidence for historic PRNP balancing selection for Kuru, but whether potential fitness costs associated with less susceptible genotypes could lead to balancing selection in cervid PRNP frequency is currently unknown (Monello *et al.*, 2017). Third, recent studies showing adaptation of prion strains (Bartz *et al.*, 1994), identified distinct strains of CWD from different species (Angers *et al.*, 2010) and different host genotypes (Herbst *et al.*, 2017) which produce different patterns of infection in mice (Velásquez *et al.*, 2015). As a possible consequence, increasing the frequency of animals with less susceptible genotypes may increase infectiousness if more hosts have similar prion conformation based on PRNP genotypes (Velásquez *et al.*, 2015). Finally, landscape-scale mixing of infected and uninfected deer populations via dispersal and/or movement may serve to

spread disease to new areas and potentially dilute 96GG PRNP genotype frequencies (Robinson *et al.*, 2012b, 2013). While increasing prevalence, population impacts, and genetic shifts in CWD-affected areas are likely, further research will be needed to clarify whether these predictions are robust and how other factors may shape future CWD dynamics and cervid management.

Pathogens pose a significant risk to worldwide biodiversity (Daszak *et al.*, 2000; Dobson, 2004; Joseph *et al.*, 2013; Johnson *et al.*, 2015; Rohr *et al.*, 2020) and can have adverse consequences for wildlife populations. When pathogens affect individual fitness there is an added potential for natural selection of less susceptible genotypes. However, documenting pathogen-driven genetic selection in wildlife populations is difficult due to potentially complex host-pathogen interactions (LaCava *et al.*, 2021). Moreover, development of strategies to manage disease-affected wildlife populations can be challenging because of the potentially complex interaction between harvest, host demographics, disease dynamics, and genetic selection. We conducted an epizootiological analysis based on >13,000 white-tailed deer harvested in Wisconsin during the early stages of a CWD outbreak. We found strong evidence for genetic selection favoring PRNP genotypes that are less susceptible to both infection and disease-associated mortality. In addition, CWD infection rates differed based on age and sex, potentially complicating future population demographics and changes in genetic composition. We used a population modeling approach to combine the epizootiological results with deer demographics to evaluate future trends in CWD prevalence, genotype frequencies, and deer abundance under differing harvest strategies. The best management strategies depend on future goals for deer abundance, genetic composition, and disease prevalence. Our results provide support for the control of CWD by aggressive harvest of adult males, which have the highest infection and prevalence rates. We found that genetic selection favoring less susceptible PRNP genotypes can be increased if population harvest is minimized. However, this strategy likely means higher future disease prevalence rates, more environmental contamination with CWD prions, and more rapid disease spread. An important caveat is that demographic data on the less susceptible PRNP 96SS genotype is unknown and could have future impacts on deer population dynamics. Current levels of deer harvest found throughout North America will

likely result in population declines, which are already evident in some areas, once CWD reaches higher levels of prevalence/infection. As CWD continues to spread in cervid populations throughout North America and worldwide, control strategies need to consider the interwoven complexity of species-specific demographics, host-pathogen interactions, and specific control measures.

Data Availability Statement

Data available via the Dryad Digital Repository https://doi.org/10.5061/dryad.866t1g1s2(Ketz,Robinson,Johns & Samuel).

Authors' Contributions

ACK and MDS conceived of the study. SJR and CJJ collected and processed genetic data. ACK, MDS, and SJR processed data and created models. ACK analysed data. All others interpreted results. ACK wrote the first draft of the manuscript and all authors contributed to revisions.

Conflict of Interest

All authors of this manuscript declare no conflict of interest.

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Table 1: Comparison of four force of infection models with different structures using Watanabe Akaike information criteria (WAIC). Force of infection (λ) could vary or be equivalent according to sex including males (m) and females (f), genotypes 96GG (G) or 96GS/SS (S), and by age classes denoted by adults (A) and yearlings (Y). Disease-associated mortality (μ) had similarly specified parameters.

Model	WAIC	Δ WAIC
$\lambda_{m\neq f}, \mu_{m=f}$	59.69	226.57
$\lambda_{m\neq f}, \mu_{m\neq f}$	2.89	169.76
$\lambda_{\mathbf{Y,m=f}}, \lambda_{\mathbf{A,m\neq f}}, \mu_{\mathbf{Y}} = \mathbf{0}, \mu_{\mathbf{A,m=f}}$	**-166.87**	**0**
$\lambda_{Y,m=f}, \lambda_{A,m\neq f}, \mu_Y = 0, \mu_{A,m\neq f}$	-161.75	5.12

Table 2: Summary statistics of the posterior distributions of the parameters from the top model (Table 1) including the mean, and equal tailed 95% Bayesian credible intervals (Lower=2.5 percentile,Upper=97.5 percentile). Annual probability of infection (ψ) and force of infection (λ) varied by sex denoted females (F) versus males (M), age classes were denoted adult(A) and yearlings (Y). Lastly, the parameters varied by genotype with the more susceptible genotype 96GG (G), and the less susceptible genotype 96GS/SS (S). Disease-associated mortality (μ) could vary by genotype but was assumed equal for both sexes, and 0 for yearlings.

Parameter	Mean	Lower	Upper
$\psi_{F,S}$	0.03	0.02	0.03
$\psi_{F,G}$	0.11	0.10	0.13
$\psi_{M,S}$	0.07	0.06	0.08
$\psi_{M,G}$	0.25	0.22	0.27
$\psi_{Y,S}$	0.01	0.01	0.01
$\psi_{Y,G}$	0.03	0.03	0.04
$\lambda_{F,S}$	0.03	0.02	0.03
$\lambda_{F,G}$	0.12	0.11	0.14
$\lambda_{M,S}$	0.07	0.06	0.09
$\lambda_{M,G}$	0.28	0.25	0.32
$\lambda_{Y,S}$	0.01	0.01	0.01
$\lambda_{Y,G}$	0.03	0.03	0.04
μ_S	1.00	0.79	1.25
μ_G	1.53	1.35	1.74

List of Figures

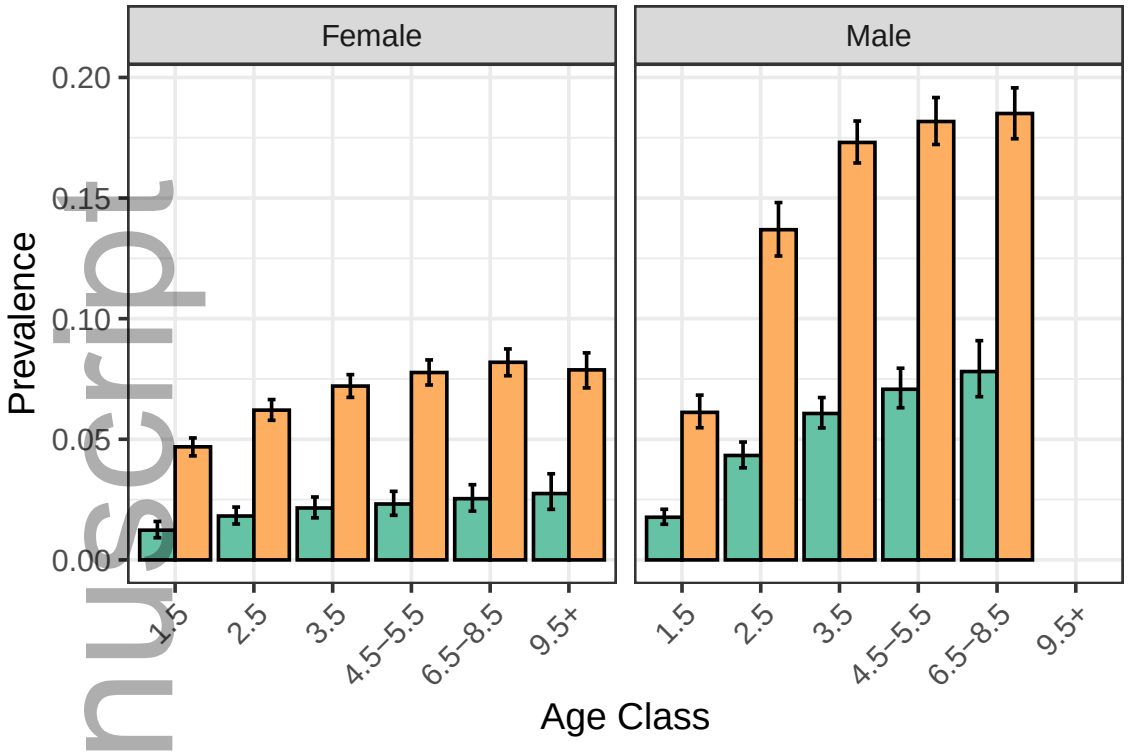


Figure 1: The posterior distributions of age-corrected CWD prevalence in white-tailed deer in south central Wisconsin, for sex (right for males, left for females), age classes, and PRNP genotype with the heterozygous and homozygous 96GS/SS less susceptible genotype (green bars) compared with the homozygous more susceptible 96GG genotype (orange bars).

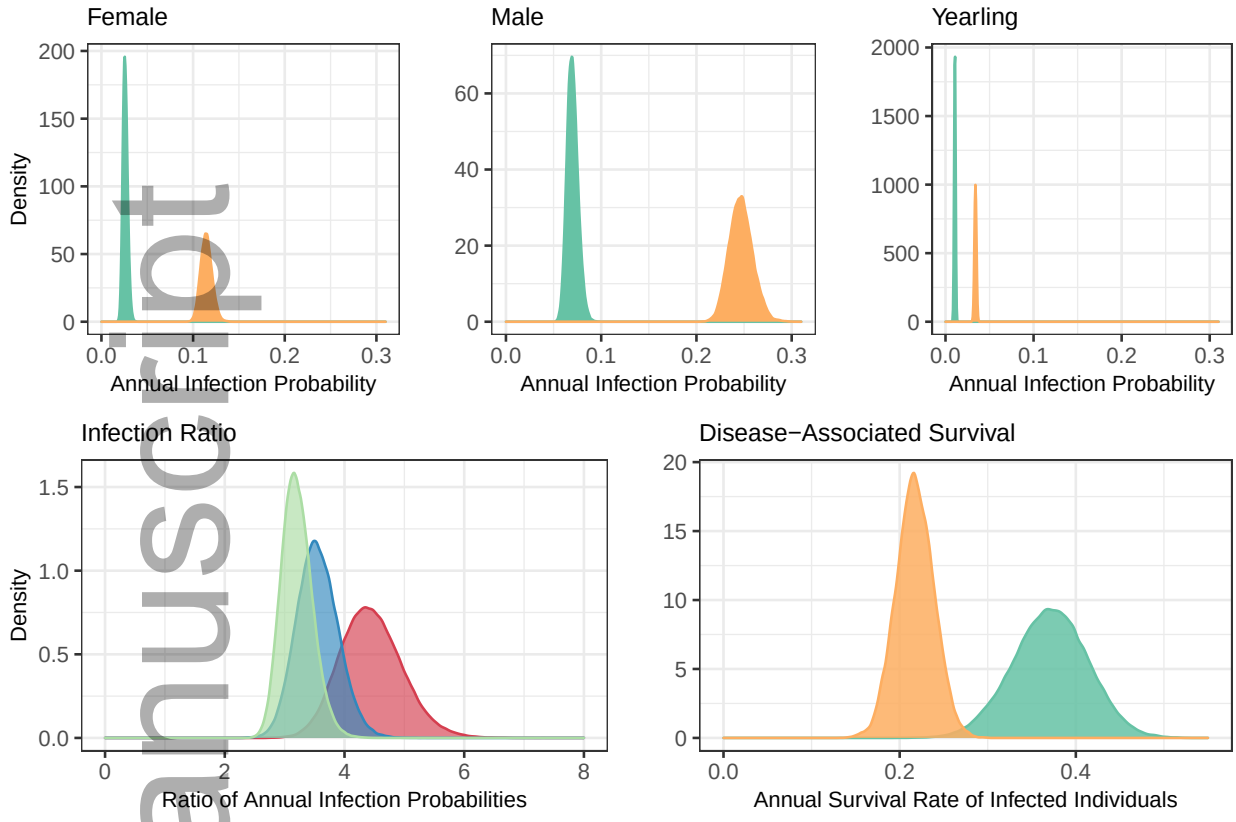


Figure 2: The top row shows the posterior distributions of the annual infection probabilities from the top model for the more susceptible genotype 96GG (orange) compared with the less susceptible genotypes 96GS/SS (green) for adult females, adult males, and yearlings. The bottom plot shows the posterior distributions of the ratios of annual infection probabilities of the more susceptible genotype (96GG) relative to the less susceptible genotype (96GS/SS) for females (red), males (blue), and yearlings (green). The bottom right shows the posterior distributions of the annual disease associated mortality for the more susceptible genotype 96GG (orange) compared with the less susceptible genotypes 96GS/SS (green).

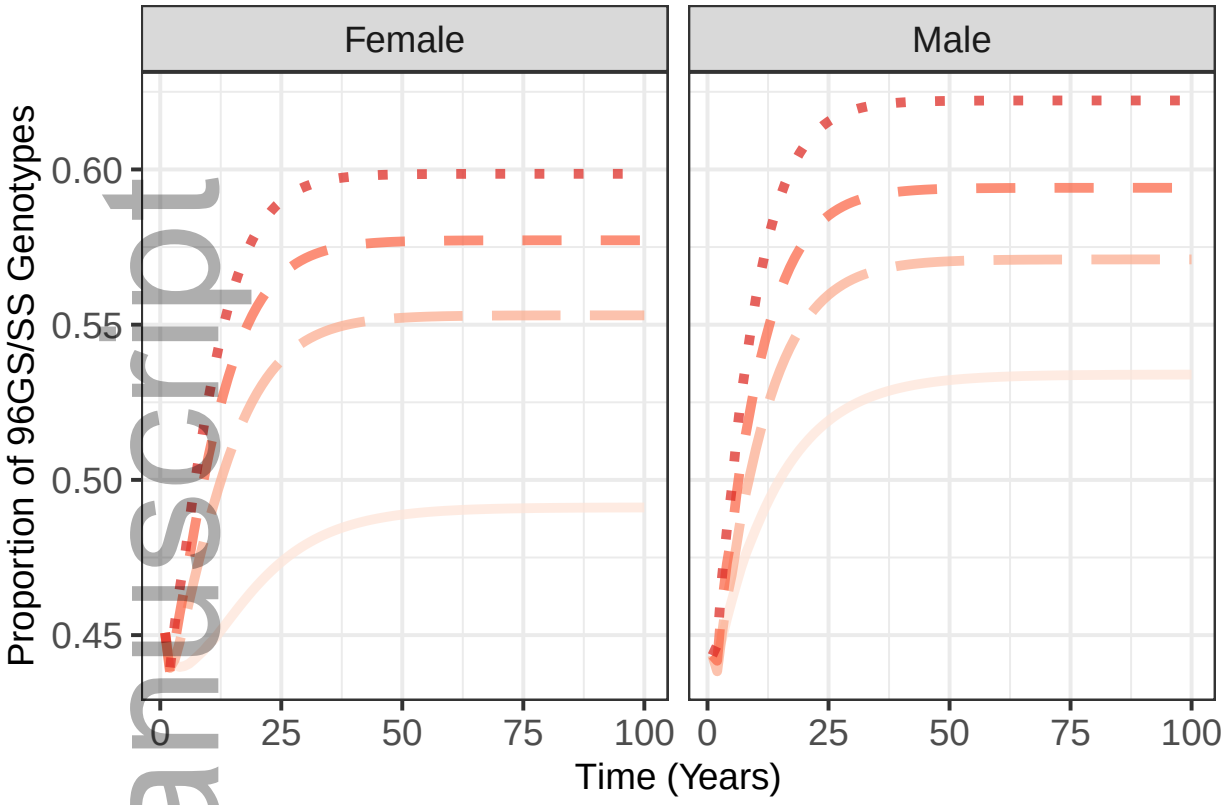


Figure 3: Simulated proportions of 96GS/SS genotypes over time (years) under different infection scenarios with antlerless and antlered hunter harvest set to 0.16. Infection rates were multiplied by a values ($\{1, 5, 10, 15\}$) to incorporate potentially increasing transmission rates over time. The infection rate indicated by the data had a multiplier of 1 (lightest red solid line) with increasing multipliers until 15 times the original infection rate (darkest red dot dash) for females (left) and males (right).

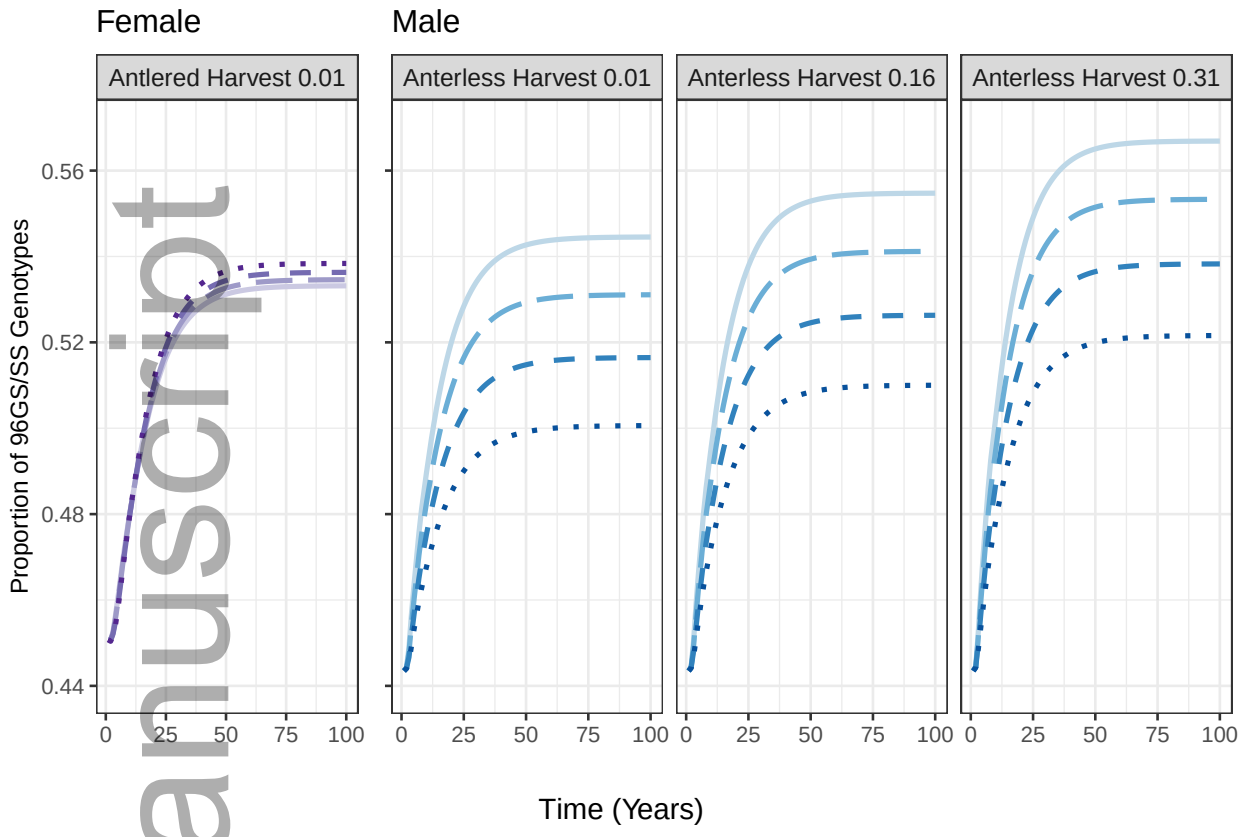


Figure 4: Simulated proportions of 96GS/SS genotypes over time (years) under different harvest scenarios. The proportion of 96GS/SS females (Left plot, purple lines) increases over time, assuming baseline infection rates, under antlerless harvest rates of .01 (solid line), .11 (dashed line), .21 (smaller dashed line), and .31 (dotted line) where increasing harvest rates are also darker. Similarly, the proportion of male white-tailed deer with the 96GS/SS genotypes increased under antlered harvest rates of .01 (solid line), .11 (dashed line), .21 (smaller dashed line), and .31 (dotted line), under three values of antlerless harvest, since juvenile males are antlerless.

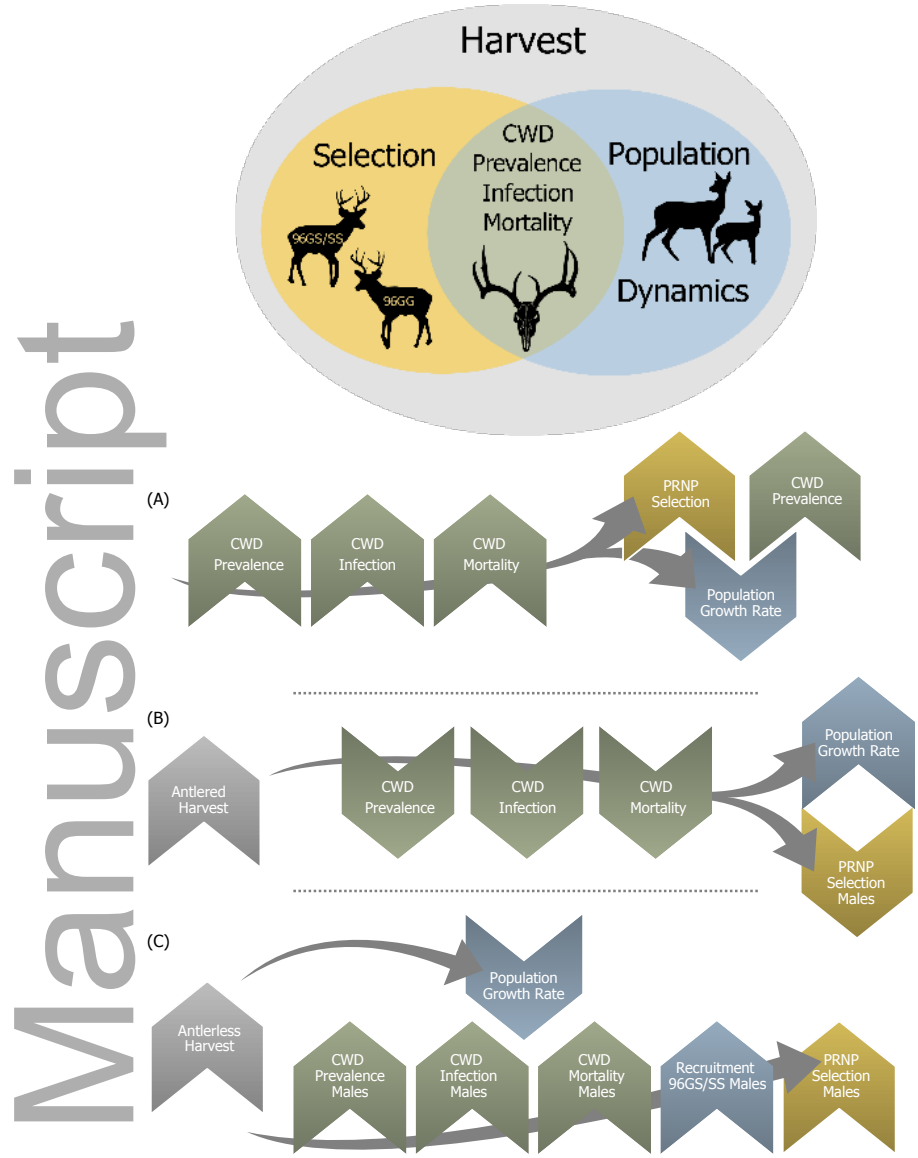
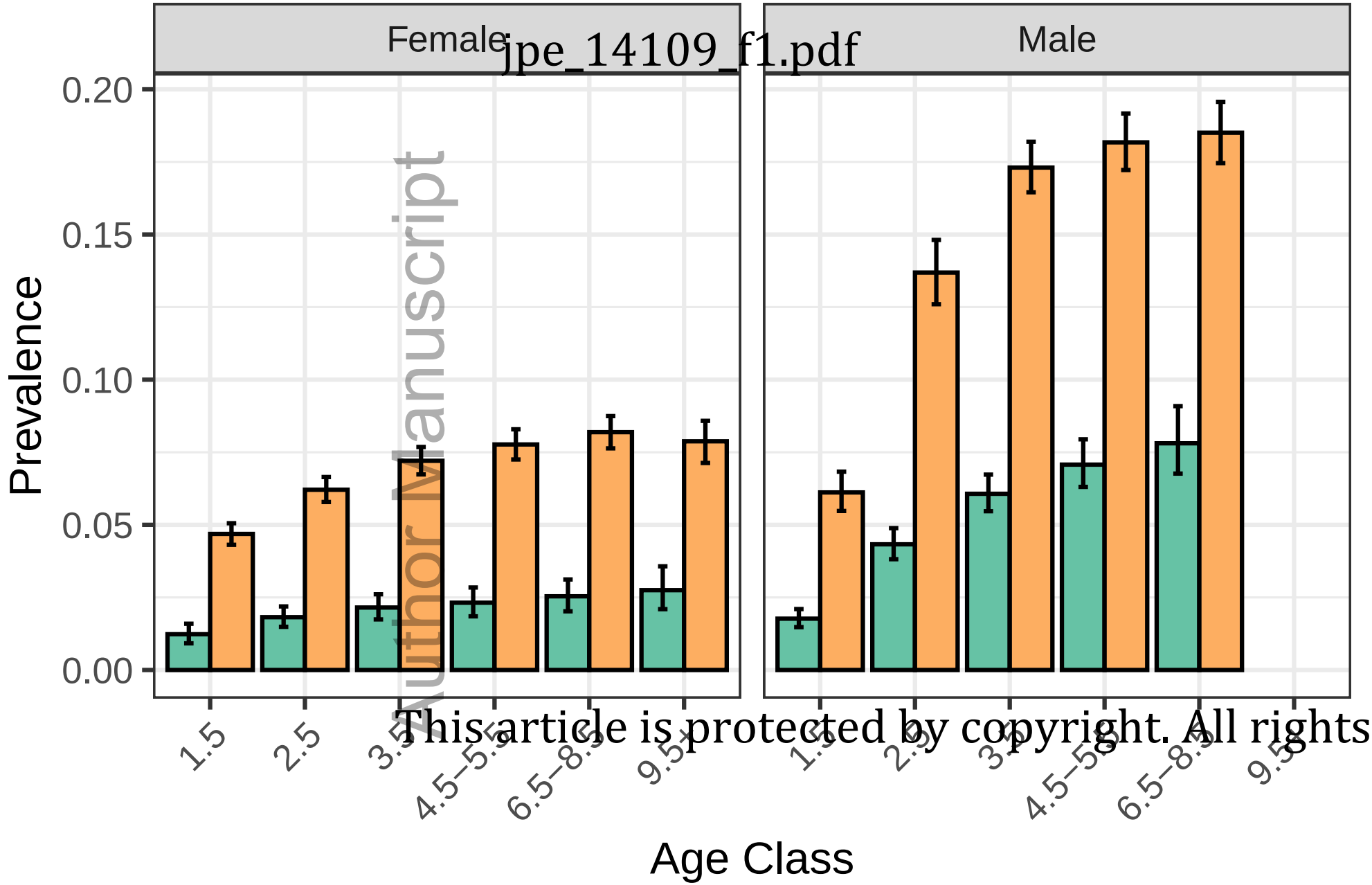
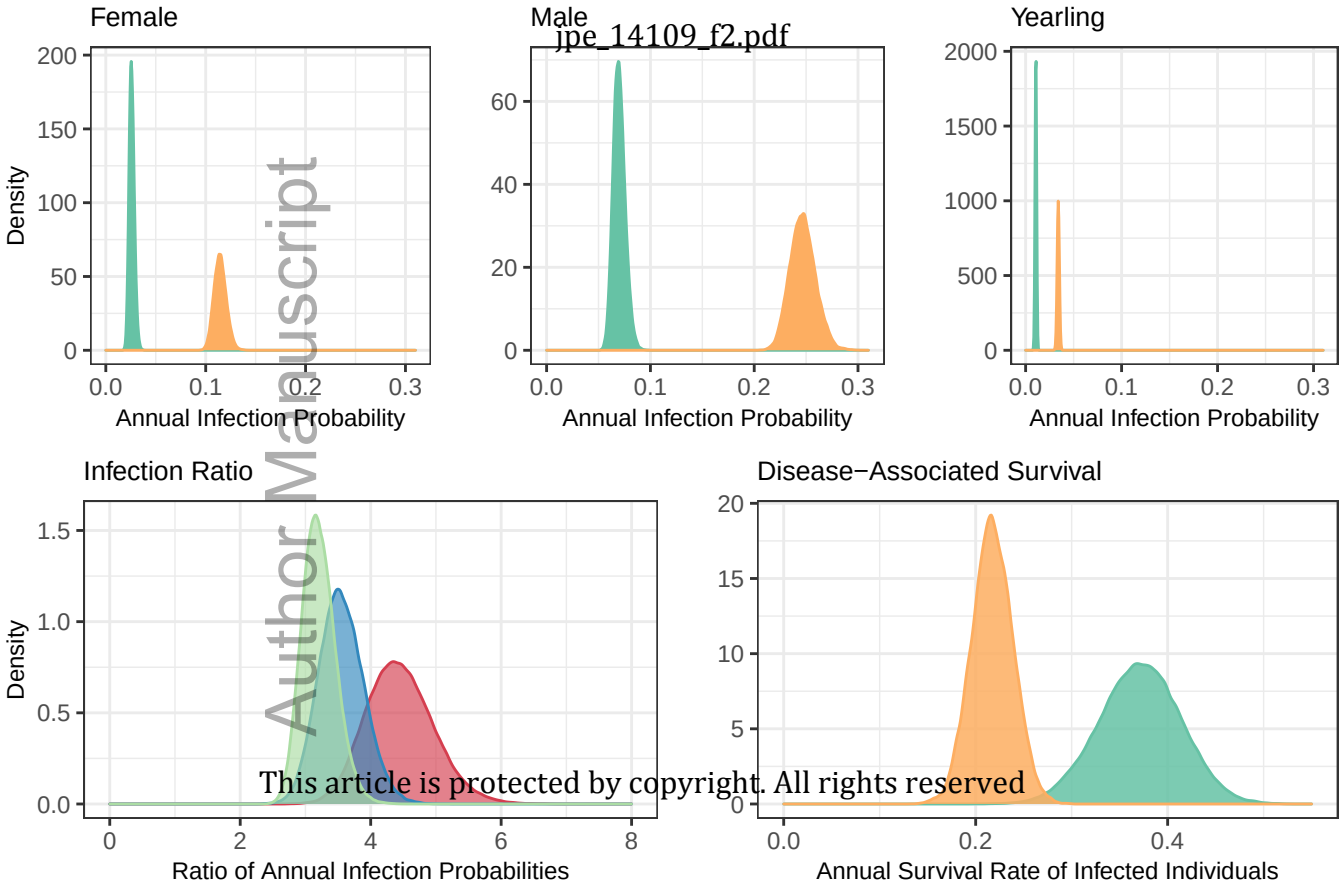
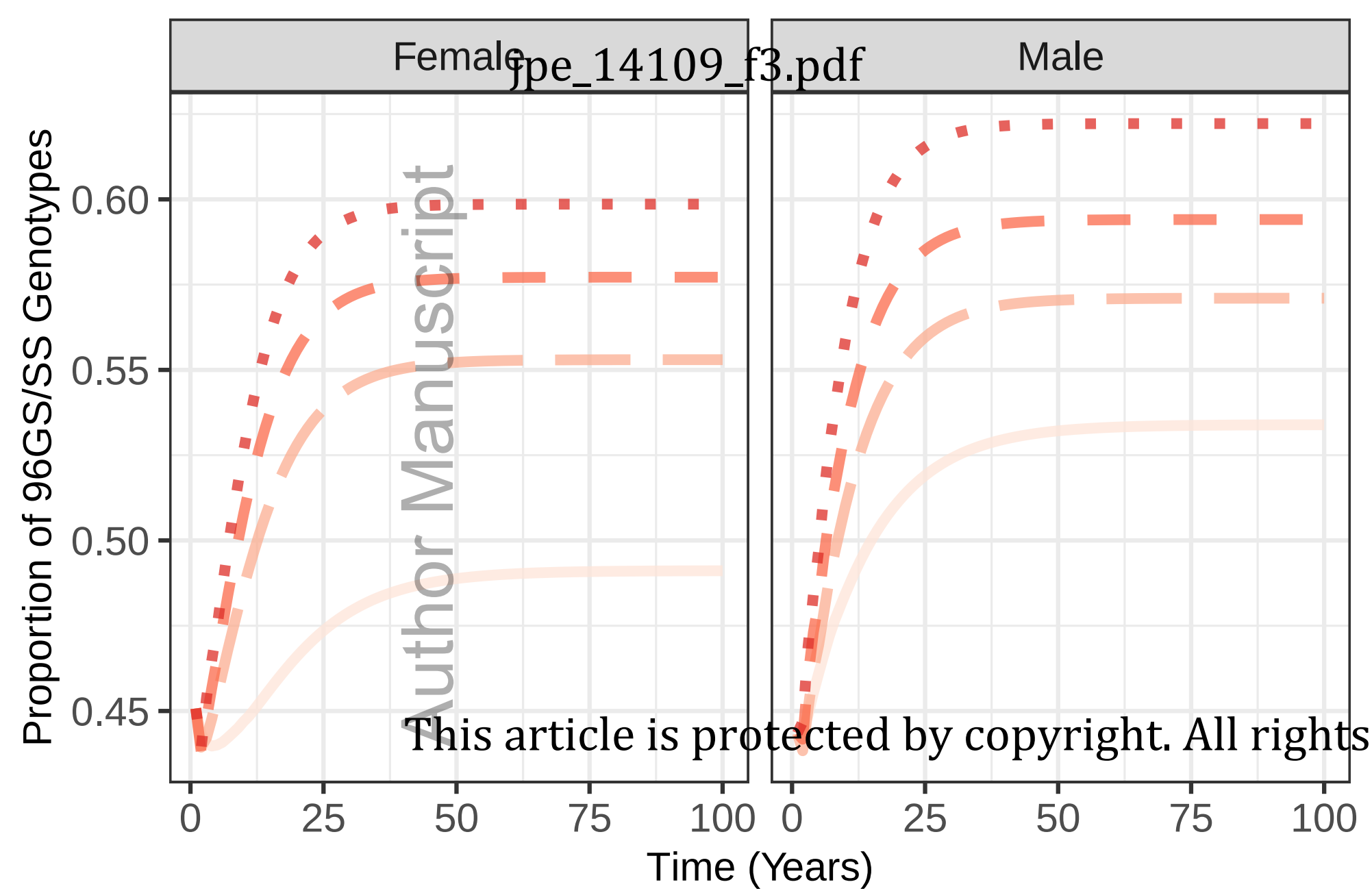
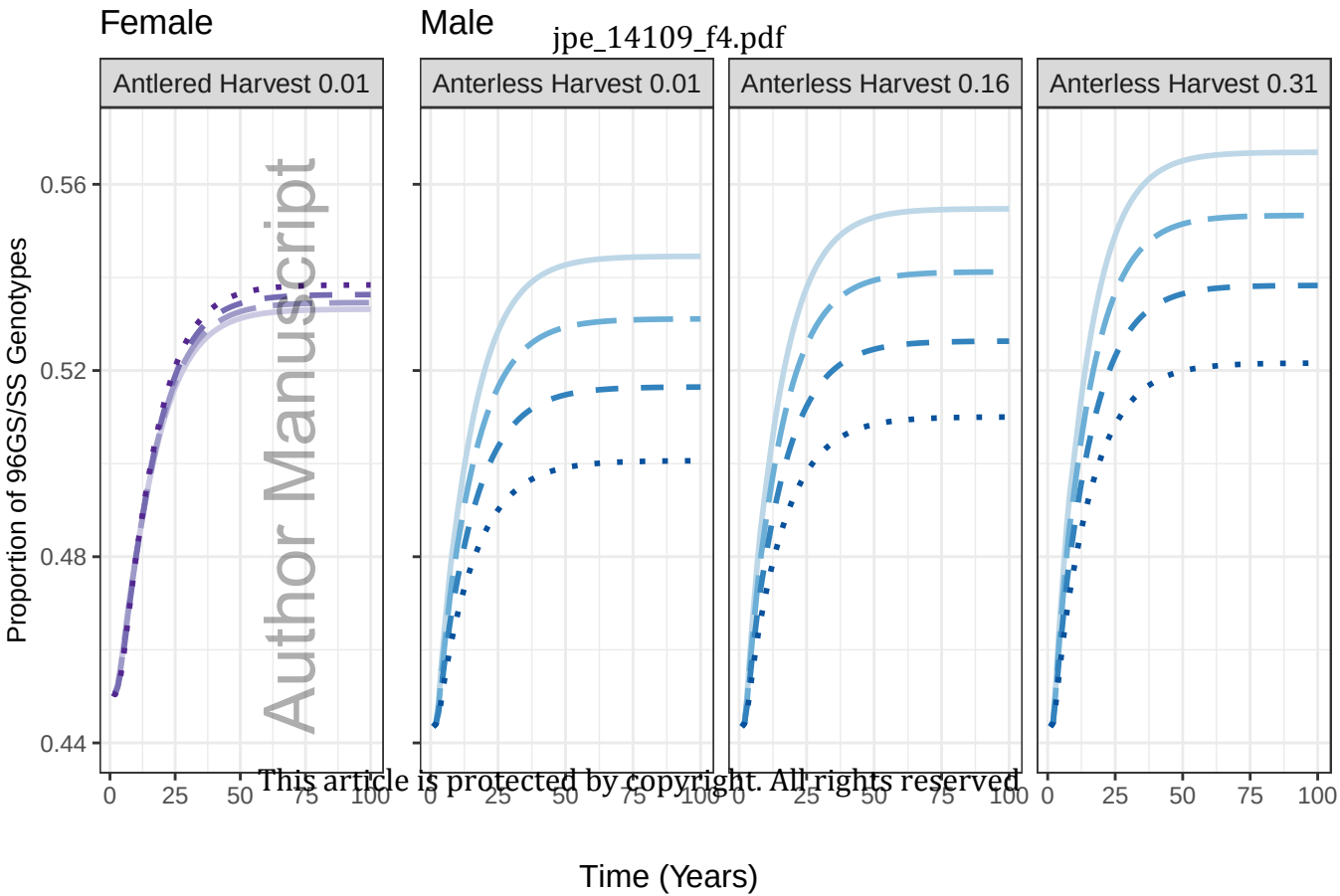


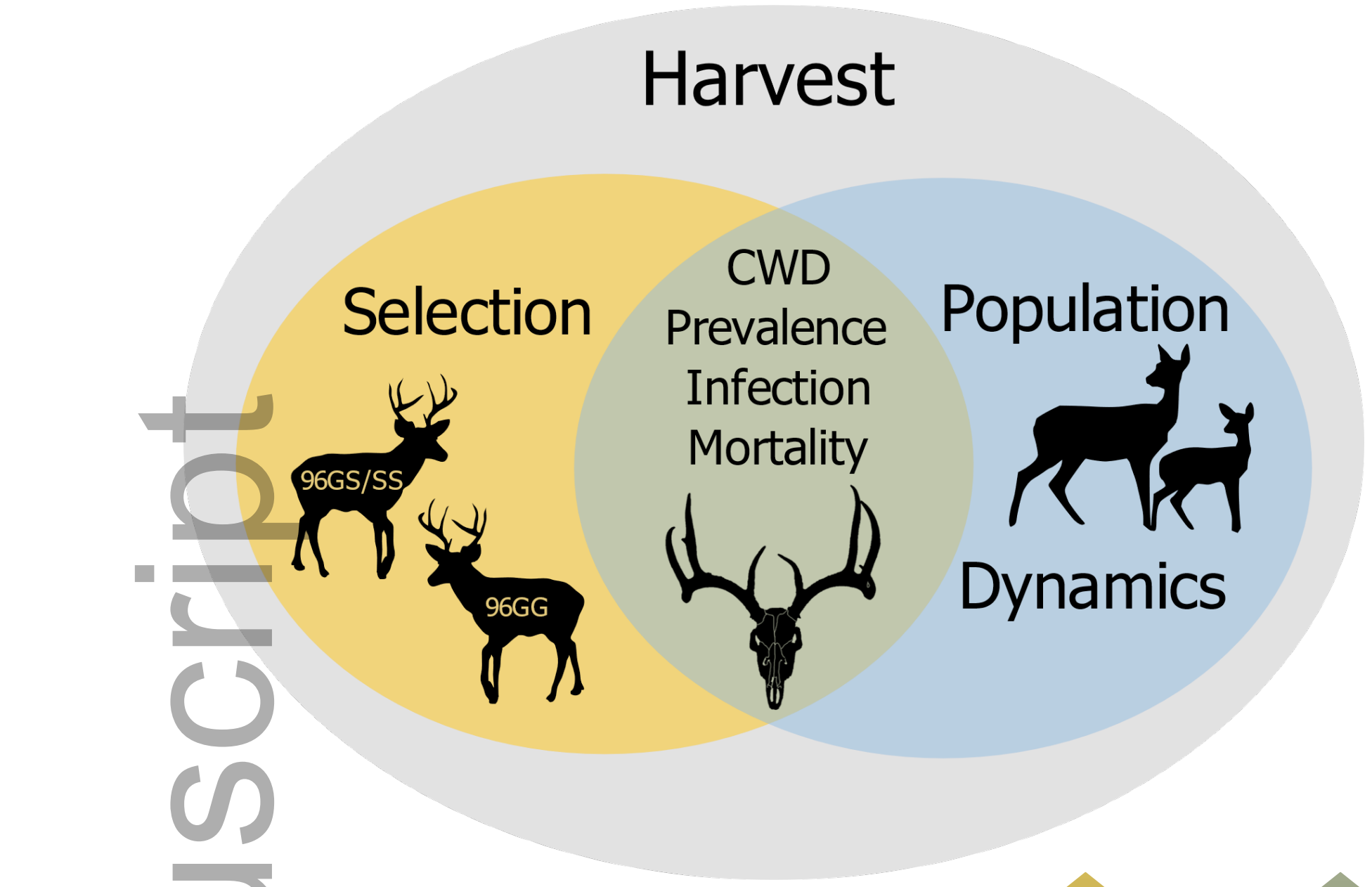
Figure 5: Chronic wasting disease (CWD) epizootics are characterized by a long period of disease establishment and slowly increasing prevalence. Once CWD prevalence reaches 5-10 percent then prevalence begins to increase exponentially. Higher CWD prevalence (A) leads to higher CWD infection and disease-associated mortality, which over time leads to population declines and increased genetic selection favoring the less susceptible PRNP 96GS/SS genotypes. Moreover, increased selection of the less susceptible PRNP 96GS/SS genotypes leads to increased CWD prevalence due to longer incubation times. Disease, genetic selection, and population trajectories were all determined by these cascading effects. Harvest mortality can also affect CWD prevalence, deer population growth, and genetic selection depending on the specific harvest strategy. Our simulations show that higher rates of antlered harvest (B) lead to lower CWD prevalence, disease-associated mortality, and CWD infection rates, which ultimately lead to higher population growth rates and lower genetic selection pressure. Higher rates of antlerless harvest (C) lead to decreasing population growth rates, as well as higher rates of genetic selection in adult males.





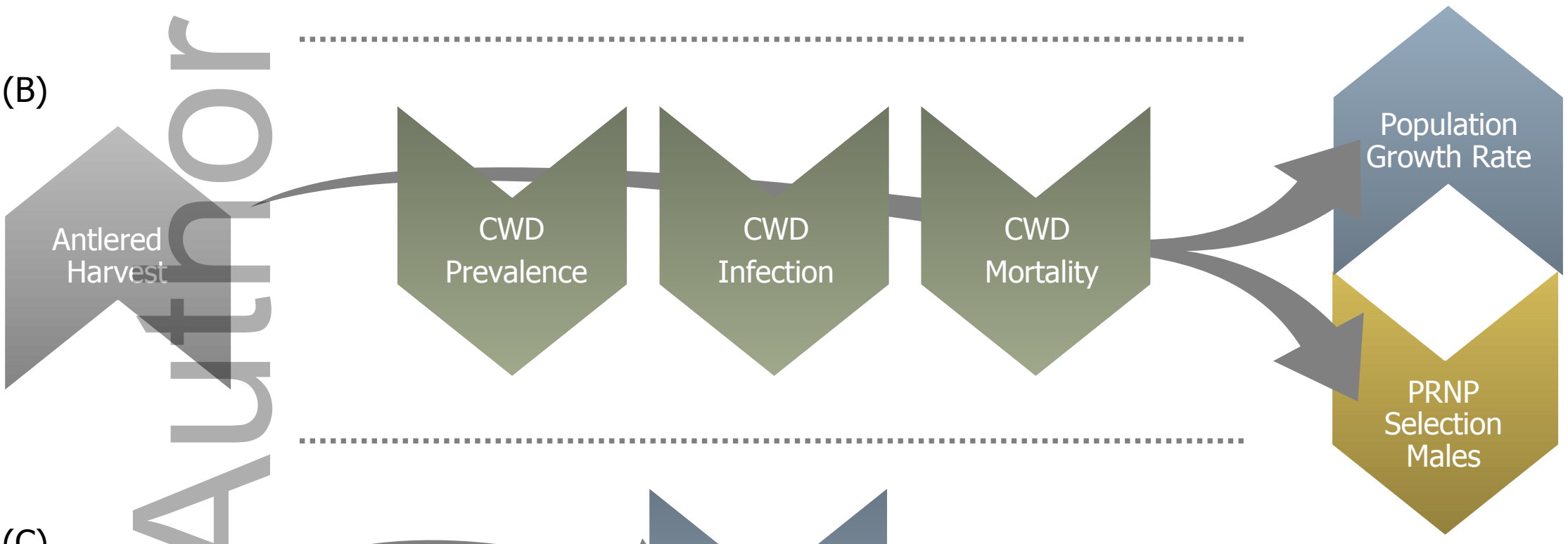






(A)

(B)



(C)