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Simulating sterilization, vaccination, and test-and-remove as brucellosis control measures in bison

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Abstract. *Brucella abortus*, the causative agent of bovine brucellosis, infects wildlife, cattle, and humans worldwide, but management of the disease is often hindered by the logistics of controlling its prevalence in wildlife reservoirs. We used an individually based epidemiological model to assess the relative efficacies of three management interventions (sterilization, vaccination, and test-and-remove). The model was parameterized with demographic and epidemiological data from bison in Yellowstone National Park, USA. Sterilization and test-and-remove were most successful at reducing seroprevalence when they were targeted at young seropositive animals, which are the most likely age and sex category to be infectious. However, these approaches also required the most effort to implement. Vaccination was less effective (even with a perfect vaccine) but also required less effort to implement. For the treatment efforts we explored (50–100 individuals per year or 2.5–5% of the female population), sterilization had little impact upon the bison population growth rate when selectively applied. The population growth rate usually increased by year 25 due to the reduced number of *Brucella*-induced abortions. Initial declines in seroprevalence followed by rapid increases (>15% increase in 5 years) occurred in 3–13% of simulations with sterilization and test-and-remove, but not vaccination. We believe this is due to the interaction of superspreading events and the loss of herd immunity in the later stages of control efforts as disease prevalence declines. Sterilization provided a mechanism for achieving large disease reductions while simultaneously limiting population growth, which may be advantageous in some management scenarios. However, the field effort required to find the small segment of the population that is infectious rather than susceptible or recovered will likely limit the utility of this approach in many free-ranging wildlife populations. Nevertheless, we encourage scientists and policy makers to consider sterilization as part of a suite of available brucellosis management tools.

Key words: bison; Brucella abortus; *brucellosis; herd immunity; sterilization; superspreading; vaccination; Yellowstone.*

Introduction

Brucella bacteria, the causative agents of brucellosis, are among the most common zoonotic pathogens worldwide (Godfroid 2002, Corbel 2006). Although reported incidence and prevalence of the disease vary widely from country to country, bovine brucellosis caused by *Brucella abortus* remains the most prevalent of the brucellar infections (Corbel 1997). In animals, the preponderance of known bovine brucellosis is in domestic livestock, though many wild mammals, and especially artiodactyls, often suffer spillover infections from domestic sources (Davis 1990, Bengis et al. 2002, Godfroid 2002). Most experts agree that brucellosis in wild animal species does not contribute significantly to any pattern of disease in livestock (Madsen and Anderson 1995). However, infected wildlife becomes an important management concern when host populations are able to sustain brucellar infections independent from domestic spillover. For *B. abortus*, several notable wildlife systems fall under this scenario including African buffalo (*Syncerus caffer*) in South Africa (Madsen and Anderson 1995, Mellau et al. 2009), wood bison (*Bison bison athabascae*) in Canada (Joly and Messier 2004), and bison (*Bison bison bison*; see Plate 1) and elk (*Cervus elaphus*) in the greater Yellowstone ecosystem in North America (Meyer and Meagher 1995, Rhyan et al. 2009, Cross et al. 2010). These sustainable infections in wildlife become increasingly important when they serve as possible sources of reinfection for domestic stock in the final stages of what are often long and expensive domestic brucellosis eradication campaigns (Madsen and Anderson 1995, Godfroid 2002).

Bison and elk in the greater Yellowstone ecosystem are perhaps the most widely publicized case of wildlife reservoirs threatening reinfection of what is otherwise

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essentially a "brucellosis-free" cattle stock (Ragan 2002). First detected in the United States in the early 1900s, by the mid-1930s brucellosis was considered the most significant livestock disease in the United States. To combat this problem, the U.S. Congress appropriated funds in the 1950s for a comprehensive national effort to eradicate brucellosis from domestic stocks (Cheville et al. 1998, Ragan 2002). An aggressive process of serological testing for brucellosis, followed by the removal of test-positive animals from the population and vaccination of test-negative animals, had nearly eliminated the disease from livestock by the early 1990s (Ragan 2002). However, *B. abortus* spilled over from cattle to Yellowstone bison by 1917 (Meagher and Meyer 1994) and spread through the population, which is now chronically infected with 40–60% of tested bison showing positive signs of exposure to this nonnative disease (Hobbs et al. 2009).

Brucellosis transmission occurs when *B. abortus*-infected birthing tissues are shed onto the landscape and contacted by susceptible animals (Thorne 2001). Elk have been implicated as the probable source of recent brucellosis transmission events to cattle (Beja-Pereira et al. 2009), but bison remain a focal point of management (U.S. Government Accountability Office 2008). From 2004 to 2010, at least one cattle herd was exposed to brucellosis each year in Montana, Idaho, and Wyoming (Plumb et al. 2009, Wyoming Livestock Board 2010). These outbreaks resulted in each state temporarily losing its brucellosis-free status. Federal brucellosis class-free status provides significant economic benefits to a state's cattle industry, including reduced costs for testing and vaccinating against the disease, and greater access to within- and out-of-state cattle markets (Kilpatrick et al. 2009).

Yellowstone bison are migratory, with most bison moving from higher elevation summer ranges inside Yellowstone National Park to lower elevation winter ranges in and outside the park. Problems arise when migration results in bison moving beyond the boundaries of designated conservation areas and onto nearby ranges where cattle summer (Meagher 1989, Cheville et al. 1998, Bruggeman et al. 2009, Plumb et al. 2009). In 2000, after nearly 10 years of negotiations, the Federal Government and State of Montana agreed to an Interagency Bison Management Plan (IBMP) that established guidelines for managing the risk of brucellosis transmission from bison to cattle through the use of hazing, test-and-slaughter, hunting, and other actions near the park boundary, when necessary (U.S. DOI, NPS, USDA-FS, and APHIS 2000*a*, *b*). The IBMP management activities are costly and controversial. A 2008 Government Accountability Office (GOA) report estimated the annual expenditure of nearly U.S.$3 million (2002–2007 adjusted for inflation to 2009 dollars) for all aspects related to bison management (U.S. GOA 2008). Under the IBMP (2001–2010), ~3200 bison have been shipped to slaughter when hazing became ineffective at keeping bison in designated conservation areas (White et al. 2011). More than 1000 bison were culled from the population during winter 2006, and an estimated 1700 bison were culled during winter 2008 (~21% and 37% of the total population, respectively; White et al. 2011).

Our objective was to use an epidemiological model to simulate the effects of different disease management strategies on brucellosis prevalence and bison population dynamics. Unlike many disease models that are "top-down," or phenomenological in nature, we utilized a mechanistic approach whereby disease dynamics are driven by mechanisms operating on individual bison (e.g., contacts per infectious event and transmission). Although a variety of management strategies exist, we focused our modeling efforts on three different management strategies suggested by the various IBMP agencies: vaccination, test-and-remove, and sterilization (U.S. DOI, NPS, USDA-FS, and APHIS 2000*a*, Rhyan and Drew 2002, Miller et al. 2004). Here, sterilization is used to directly impact infectious events (e.g., abortions, still births, retained placentas) associated with pregnancy and not as a population control device with the intent of reducing host density.

Our conceptual framework for applying management strategies was built around the operational tools available to wildlife managers: age classification and serological status. Due to the diagnostic limitations to identifying and treating infectious individuals in the field, current anti-mortem tests rely on serological results. Serology only provides indirect evidence of infection because it detects antibodies rather than living bacteria, and thus, cannot differentiate between infectious and recovered individuals. The biology of brucellosis in ungulates, however, allows management efforts to be more targeted. Males and pre-reproductive females are unlikely to transmit infection (Cheville et al. 1998), and old seropositive females are more likely to be recovered than infectious. Thus, young reproductive females (3–5 year olds for bison) are presumably driving much of the disease dynamics. We explore the effects of "target selectivity" for each management strategy by using different seroprevalence and age–class combinations as management targets.

The current brucellosis vaccine for cattle, Strain RB51, is effective in preventing clinical brucellosis symptoms (e.g., abortions and infectious live births), but will not result in positive reactions on serologic tests. Consequently, vaccinated bison will remain test negative unless exposed to field strain *Brucella* following vaccination (Olsen et al. 2009, 2010). Although the vaccine is expected to reduce *B. abortus* shedding and subsequent transmission and not influence serologic results (i.e., create false positives), it will not prevent subsequent seroconversion upon exposure to *B. abortus*.

Finally, the logistics of implementing domestic disease control strategies in wildlife are often difficult in a wild setting (Rhyan and Spraker 2010). Accordingly, we

tracked the effort required to implement various strategies including the number of animals handled and the amount of serological testing. While our measure of effort does not relate to the actual cost of managing brucellosis in bison, it does provide a relative measure which can play a vital role in choosing between inexpensive, weak controls that lead to smaller and slower changes in disease prevalence, or expensive (but perhaps more cost effective) controls that lead to faster and larger management impacts (Keeling and Rohani 2008).

Methods

We used a stochastic, individual-based modeling approach following the structure of Gross et al. (1998) and Treanor et al. (2010) to account for *B. abortus* transmission dynamics each year from January 1 through the last birthing event on a weekly time step, and then adjusted for annual reproduction and survival (Fig. 1A). We allowed the model to stabilize for the first 14 years, applied management actions starting at year 15, and tracked model output through 35 years of consecutive treatment.

We used estimates of age-specific pregnancy rates and survivorship, growth rate (λ), and stable age distribution for the Yellowstone bison population to seed the initial population model (Table 1, Fig. 1; Fuller et al. 2007*a*). For the case of Yellowstone bison, it is difficult to compare management strategies in the absence of any removals because this has been the primary mechanism of population regulation for several decades (Cheville et al. 1998). We assumed that the bison population was limited to 1600 yearling and adult females through an annual removal process. At the beginning of a simulation year (i.e., Jan 1) the number of adult and yearling animals above the threshold (1600) was calculated and this determined the number of animals for non-disease-related removal. These removals were spread evenly over the first two months to simulate the timing of boundary removals and individuals were selected randomly from the population without respect to disease status. This approach does not capture the stochastic variation of actual bison removals, but enables a more direct interpretation of differences among management strategies. Pregnant bison were assigned a random conception week from a truncated normal distribution with peak conception occurring at week 30.5 over a span of 9 weeks (range 26–35). These conception dates, coupled with a 41-week gestation period, provided a time span of birthing events similar to that observed in wild bison (Berger and Cain 1999, Walde 2006, Jones et al. 2009).

We used a weekly time step to model the transmission season, which we assumed overlapped the third trimester of pregnancy when abortions and births typically occur (Cheville et al. 1998, Jones et al. 2010, Treanor et al. 2010). We tracked disease dynamics by classifying bison as susceptible, exposed, infectious, or recovered (SEIR; Fig. 1B; Keeling and Rohani 2008). Following exposure, susceptible individuals enter an exposed class, which lasts for five weeks (Gross et al. 1998) and terminates with transition into the infectious class. For the duration of an infectious pregnant bison's third trimester, the fate of the fetus during each time step followed a Bernoulli process, where independent but identical weekly Bernoulli trials for abortion with probability δ (Table 1) determined if an abortion occurred. After an abortion, individuals may either remain in the infected class based on the probability of recovery γ or transition to the recovered class. Bison that did not abort during the annual time step may shed bacteria during a live birth with probability ψ before moving to the recovered class. We defined the recovered class in our model as having immunity to *B. abortus* challenges, but allowed these recovered individuals to recrudesce back to the infectious class with probability ω following a Bernoulli structure (Table 1). Once an animal recrudesced, they were indistinguishable from more recent seroconverters (i.e., individuals moving from susceptible to infectious class; Rhyan et al. 2009).

We incorporated bison group size (M. Meagher, *unpublished data*) and mixing rates into the disease dynamics during the model development phase. For social mammals (Bonabeau et al. 1999), including bison (M. Meagher, *unpublished data*), group size typically follows a power law distribution that is influenced by overall population abundance. Also, data suggest that group stability is low for bison (Lott 1991, Fortin et al. 2009). From the perspective of a disease that typically has a long latency period between contact and subsequent transmission (i.e., spanning biological seasons) the fluid group structure of Yellowstone bison diminishes the role of group structure by decreasing the potential for strong infection heterogeneity between bison social groups. Accordingly, we used well-mixed groups in the model, but retained group structure for sensitivity analysis, which showed that group size and mixing rates were relatively unimportant unless group sizes were uniformly distributed or mixing rates were very low (0.05% groups change per week).

While group structure is an obvious part of bison behavior, the distribution of contacts with infectious material (i.e., transmission) plays a more critical role in disease dynamics. We determined the number of bison contacting each infectious event by drawing from a negative binomial distribution fitted to empirical contact data (Jones et al. 2009, Treanor et al. 2010). The contact data are the number of bison inspecting a live birth, which we used as a proxy for contacts with infectious material. Bison contacts with live births were heavily right skewed, whereby many births had few or zero contacts and a few births had many contacts (Fig. 2). Use of such long-tailed contact distributions may be important for capturing the rare but large transmissions that may occur when females retain placentas (lasting as long as three days and for distances exceeding 5 km), or abortions happen in places where infectious material

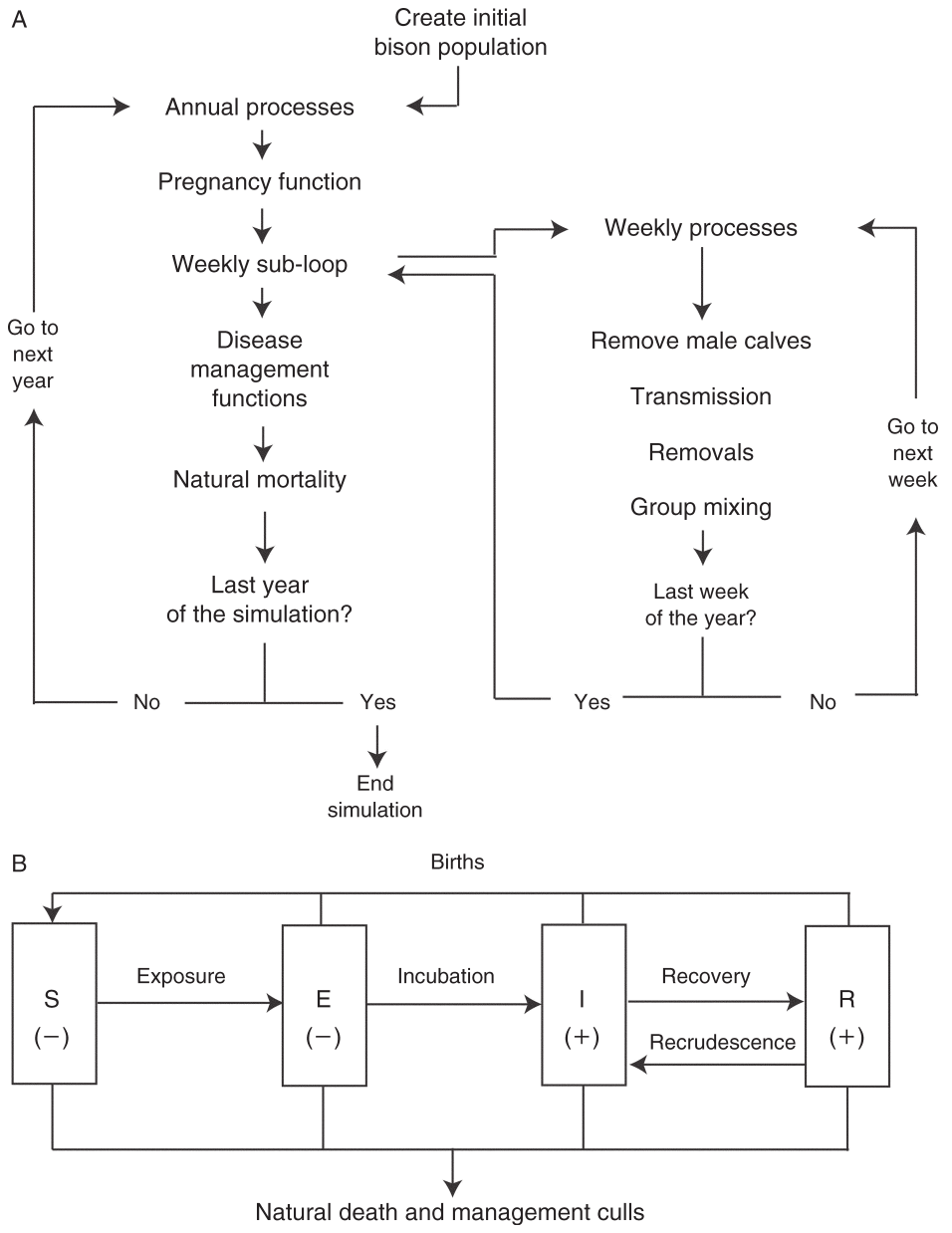

FIG. 1. (A) Flow diagram of annual and weekly model processes for a single simulation with bison (*Bison bison bison*). (B) Simple schematic of movement pathways between compartments for the disease sub-model without management action. Management treatments result in permanent removal of individuals into either a sterilized or vaccinated compartment (not shown) where they cannot transmit *Brucella abortus*. Positive and negative symbols below compartment letters indicate the assumed serological status of all individuals in the compartment.

persists for extended periods in the environment (Corbel 1989, Jones et al. 2009, 2010).

We mechanistically modeled transmission by drawing the number of contacts per infectious event and, for those contacts that were with susceptible bison, conducting a Bernoulli trial with probability φ to determine who was infected, where φ is the probability of transmission given contact (Table 1). The necessary data do not currently exist to correlate the number of contacts with bison group size, although such a relationship may exist. Restricting the number of contacts by group size (i.e., truncating random draws from the contact distribution by group size) would have altered the realized contact distribution for a given simulation from the intended distribution (e.g., empirical fit). Therefore, contacts were first randomly assigned to those in the same group and then if the number of contacts was greater than the group size contacts were randomly assigned to others in the population. We explored additional distributions including Poisson and other negative binomials representing

TABLE 1. Model parameters, symbols, and sources used in the simulation model.

Parameter and abbreviation	Value	Source
Pregnancy rate (PRG_x)†		
<3 yr olds	0.00	Fuller et al. (2007*b*)
3 yr olds	0.714	Fuller et al. (2007*b*)
>3 yr olds	0.904	Fuller et al. (2007*b*)
Calving rate (CLV_x)†		
<3 yr olds	0.00	Fuller et al. (2007*b*)
3 yr olds	0.625	Fuller et al. (2007*b*)
>3 yr olds	0.816	Fuller et al. (2007*b*)
Survival rate (SRV_x)†		
Calves	0.760	Kirkpatrick et al. (1996)
Non-calves	0.922	Fuller et al. (2007*b*)
Gestation length (gest)	41 weeks	Reynolds et al. (2003)
Probability of abortion, if infected and pregnant (δ)	0.960	Olsen and Holland (2003), Treanor et al. (2007)
Probability of recovery given infectious event (γ)‡		
High	0.90–1.00	varied across simulations
Medium	0.70–0.80	varied across simulations
Low	0.50–0.60	varied across simulations
Probability of transmission given contact (φ)	0.93–1.00	varied across simulations
Probability of recrudescence (ω)§		
High	0.20–0.25	varied across simulations
Low	0.05–0.10	varied across simulations
Probability of infectious live birth if no abortion (ψ)‡	0.66	Gross et al. (1998)

† The subscript x is age class.
‡ Single event probabilities.
§ Expressed as annual value, but weekly values are used in the model.

fewer zero contacts and longer tails to simulate more extreme heterogeneity in contacts/infectious event (Appendix A: Fig. A1).

Male births were included in the model to account for abortions and infectious live births from male fetuses and offspring. We considered mothers and calves as a single unit for several months (male $\bar{x} = 9$ months; female $\bar{x} = 14$ months), whereby if the mother contacted a fetus so did her calf, because this matched the way the contact data were collected (Treanor et al. 2010). Once the mother–calf bond was broken, male calves were removed from the model. Adult males are typically not present at birthing locations and thus are not represented in the empirical contact data.

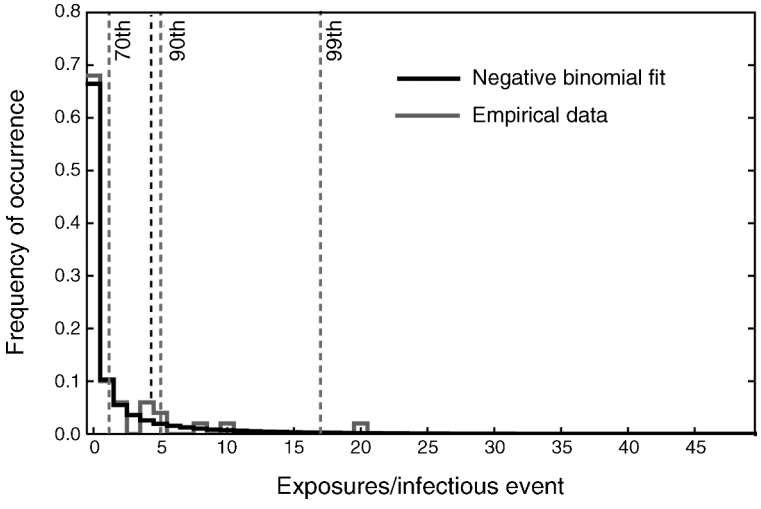

FIG. 2. Comparison of the empirical and fitted bison contact distributions. The empirical data are based on 50 observations of bison investigating live births (Treanor et al. 2010), and the fitted distribution is a negative binomial ($r = 0.17$, $P = 0.11$). Vertical lines show the 70th, 90th, and 99th percentiles: The black dashed lines are the percentiles for the negative binomial, and the gray dashed lines are the percentiles for the empirical data. The gray lines are directly on top of, and thus mask, the black lines for the 70th and 99th percentiles, showing the close fit between the negative binomial and the empirical data.

PLATE 1. Bison calf. Photo credit: Rick Wallen/NPS.

We considered the probability of recovery (δ), moving to the recovered class after an infectious event, and the probability of recrudescence (ω), moving from the recovered state back to an infectious one, to be unknown or poorly estimated and explored the sensitivity of management actions to different levels of these parameters (Table 1). We also varied the probability of transmission given contact (φ). To determine reasonable parameter combinations, we randomly selected values for all parameters from a uniform distribution and ran models without any management actions.

We compared several summary statistics to model results as a way of discarding parameter sets that were implausible. First, annual seroprevalence of brucellosis in bison has varied between 0.40 and 0.60. Second, Roffe et al. (1999) found that 46% of 26 seropositive samples were culture positive, where culture positive status is currently the best indicator of recent seroconversion and whether an individual may be infectious (Rhyan et al. 2009). Thus, we used the 95% confidence intervals surrounding the 46% estimate (0.29–0.65) as a feasible range for the proportion of seropositive bison that were actually infectious as opposed to recovered. Finally, bison population growth rate estimates have ranged between 1.05 and 1.07 from 1990 to 2001 (Fuller et al. 2007*a*, *b*). Parameter combinations that yielded model results falling within the above ranges for all three summary statistics were considered plausible scenarios for endemic disease dynamics. We ran 800 simulations of random parameter combinations for each contact distribution to produce a subset of plausible parameter combinations for each distribution.

Although moderate to low levels of transmission given contact (φ) were able to produce plausible results, our knowledge of brucellosis suggested that the massive number of *B. abortus* in birthing fluids and aborted material in combination with the strong attractant effect of expelled fetal membranes (Cheville et al. 1998) should translate to a high probability of transmission given contact with an infectious event. We allowed this parameter to slightly vary, so as to facilitate the fitting of the other parameters, but required it to remain relatively high (range = 0.925–1.000) across all parameter combinations and contact distributions. Rhyan et al. (2009) cultured *B. abortus* from some bison up to three years after seroconversion, and observed a large variation in subsequent reproductive outcomes of seroconverters, including a small proportion that had reproductive failures for four years after infection. We allowed this data set to guide our selection for the baseline recovery probability. We set this parameter to vary between 0.725 and 0.775 across all contact

distributions, resulting in probabilities of remaining in the infectious class after reproductive failure to be approximately 0.25, 0.063, and 0.016 for 2, 3, or 4 consecutive years, respectively. We used two ranges for the probability of recrudescence (ω) from the recovered class; a "low" recrudescence (5–10% chance per year) and a high recrudescence level (15–22% chance per year; Appendix A: Table A1). The recrudescence rate (ω) interacts with probability of recovery (γ), where if one is high the other must also be high to keep the summary statistics (i.e., proportion of seropositive bison that are infectious, seroprevalence, and population growth rate) within plausible ranges.

Management actions

We simulated test-and-remove, vaccination, and sterilization strategies. We assumed 100% efficacy and life treatment effects for vaccination and sterilization, and that all treated individuals were protected from abortion and/or infectious live births until death (i.e., lifetime coverage). We further assumed that vaccinated and sterilized animals did not become infected and develop antibodies after contacting infectious material (alternatively, that they were distinguishable via serological test or physical markings). We realize that brucellosis vaccines have imperfect efficacy and provide only limited protection against infection and seroconversion after exposure to virulent *B. abortus* strains (Olsen et al. 2009, Treanor et al. 2010). However, we made this assumption in an effort to contain model complexity and aid in comparisons with other treatment types that had lasting effects (sterilization and lethal removal). Furthermore, issues with efficacy of vaccination should be easily translatable to our general results (e.g., if the objective is 100 vaccinations, a 75% vaccine efficacy means you would have to treat 133 individuals to achieve the objective).

Each strategy was applied at three different annual objective treatment levels (50, 75, and 100 individuals per year for 35 consecutive years). Objective levels represented the number of individuals that managers attempt to treat each year. We refer to these as "objectives" as they were often not achievable every year if the strategy required the treatment of seropositive individuals. Once management successfully reduced the number of seropositive bison in the population to below the objective level, complete treatment was not possible. The inability to achieve an objective level was a larger issue for selective treatment based on both age and serology, which we cover in the following sections.

We also modeled selective and nonselective management strategies. For test-and-remove and sterilization, selective approaches focused on pre-reproductive seropositive animals, which are likely to be infectious at some point in the future, typically upon first pregnancy following infection. Test-and-remove and sterilization approaches applied nonselectively treat any seropositive bison regardless of age. For vaccination, selective management involves the vaccination of seronegative female calves to provide protection as soon as possible. Nonselective vaccination attempts to mimic a remote vaccination scenario where no serological test is involved. However, we restricted the target to female calves to make more straightforward comparisons to the selective treatments. We can draw conclusions on how remote delivery would work on all calves by assuming that 50% of the treatments would be male calves.

We also tested a suite of mixed strategies (i.e., vaccination and sterilization, vaccination and test-and-remove) to evaluate if they enhanced the use of vaccination in isolation. For these strategies, we used objective treatment levels of 50, 75, or 100 bison per year and applied vaccination to test-negative bison and sterilization or lethal removal to test-positive bison within the target group. Mixed strategies do not have selective and nonselective application since all individuals are treated. Instead, we used two different types of target groups for mixed management: (1) pre-reproductive females and (2) females of any age.

The proportion of bison with antibodies indicating *B. abortus* exposure (i.e., seroprevalence) can be used to quantify and compare the efficacy of different brucellosis reduction strategies, but results can be misleading unless two additional metrics are provided: (1) the number of individuals treated and (2) the effort expended to find these animals within the population. We quantified the proportion of the objective level treated during each year of management. The amount of effort required to implement a given strategy involves the amount of serological testing needed to treat a given objective level. We used the ratio of bison handled to bison treated as an index of effort. The effort index was 1 for strategies that ignored serological status (e.g., remote vaccination and mixed vaccination strategies) where treatments were applied to every individual within the target group. We assumed that managers would be unaware of the true seroprevalence in the population and would continue serological testing until either all individuals were tested or the objective level was achieved. Thus, strategies unable to meet the objective treatment levels result in high effort indices. By using our effort index as a measure of efficiency, we deliberately ignored the time required to capture individuals or the monetary expense of treatment, which are highly variable and situation specific. Thus, to achieve generality, we restricted our discussion to the number of animals handled and treated, and allow the reader to apply cost estimates to weight efficiency in a case-specific fashion (Hobbs et al. 2000).

For each contact distribution, each management category received 12 simulation types (three objective treatment levels by two selectivity levels [low, high] by two recrudescence levels [low, high]). Each simulation type was replicated 40 times and all simulations were conducted in MATLAB version 7.6 (Mathworks 2008).

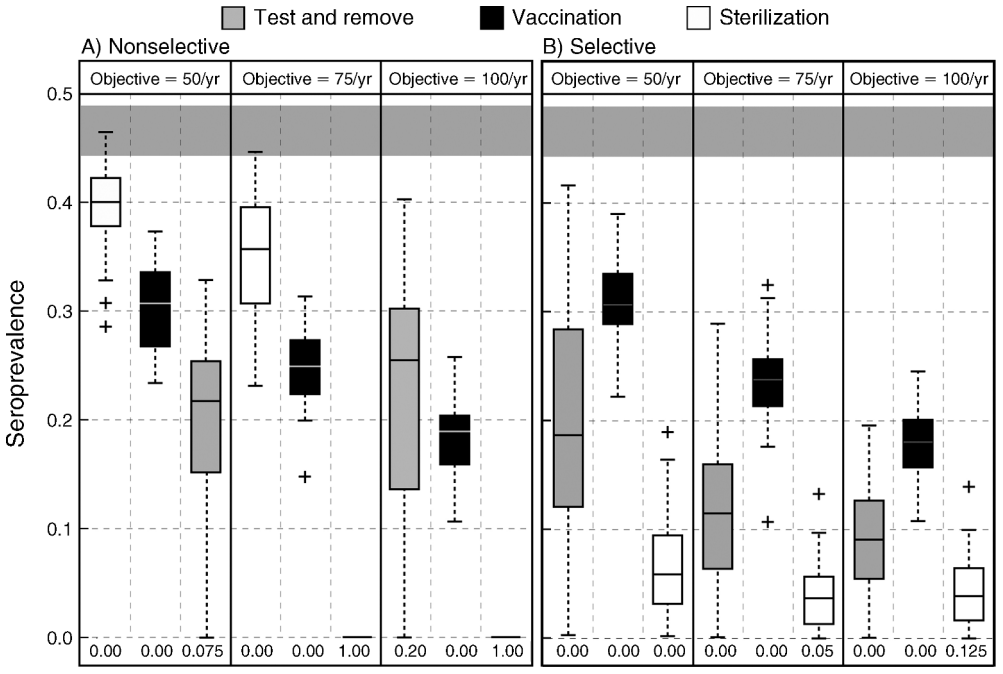

FIG. 3. Boxplots of seroprevalence after 35 consecutive years of treatment under low recrudescence for (A) nonselective and (B) selective applications. Objective is the intended number of bison to be treated for disease management in a given year. Numbers below each boxplot indicate the proportion of simulations ($N = 40$) that resulted in true eradication. The boxes represent the interquartile range (IQR), with the line bisecting the box equal to the median. The whiskers extend to 1.5 times the IQR, and points beyond the whiskers represent outliers. The gray bar at the top of each plot is the interquartile range for reference simulations (i.e., no management actions).

RESULTS

The reductions in seroprevalence were often highly variable within a given parameter set, but sterilization was generally more effective at reducing seroprevalence than either test-and-remove or vaccination for a given objective level. Nonselective sterilization outperformed selective sterilization when 75 or 100 bison per year were treated; achieving 100% eradication before the 35 years of treatment was complete (Fig. 3). Differences in selectivity increased with the magnitude of reduction in seroprevalence and were most common for test-and-remove management (Appendix B: Figs. B1–B3). The high portion of calves that were seronegative made nonselective and selective vaccination almost indistinguishable in their ability to reduce seroprevalence. However, when nonselective vaccination included all ages, a higher percentage of vaccinations were ineffective because they treated seropositive animals and seroprevalence was ~6–8% higher at the end of simulations.

When compared to vaccination alone, mixed strategies showed improvement when applied to pre-reproductive individuals and this effect increased with treatment levels (Appendix B: Fig. B4). Mixed strategies showed little difference in mean seroprevalence (±5%) regardless of which treatment was applied to test-positive bison, suggesting that over the course of time (35 years of treatment) vaccination was the primary factor influencing dynamics.

Vaccination and mixed strategies resulted in 100% of the objective treatment level being met for both selective and nonselective approaches across all treatment levels. By treating only seropositive animals, selective test-and-remove and sterilization result in very high handling to treatment ratios as seroprevalence declined (Fig. 4; Appendix B: Fig. B5). Nonselective test-and-remove and sterilization resulted in lower handling to treatment ratios compared to selective strategies (Fig. 4), but because nonselective applications also focused only on seropositive individuals the handling to treatment ratio was high when seroprevalence was low.

The effort required for different management strategies was dependent on seroprevalence and whether management targeted seronegative or seropositive animals. If objective levels were not met during management treatments, then all individuals in the target group eventually were tested and handled-to-treated ratios became very large. This issue only arose for strategies that treated seropositives and were successful at reducing their prevalence in the population (Appendix B: Fig. B.6). As seroprevalence dropped to <10%, sharp increases in effort occurred and handled to treated ratios sometimes exceeded 1000:1 due to the effort required to find the last few seropositive animals in the population.

We considered index values >50:1 to be of little interest to managers, as their sustained application seems impractical, if not impossible. Therefore, we

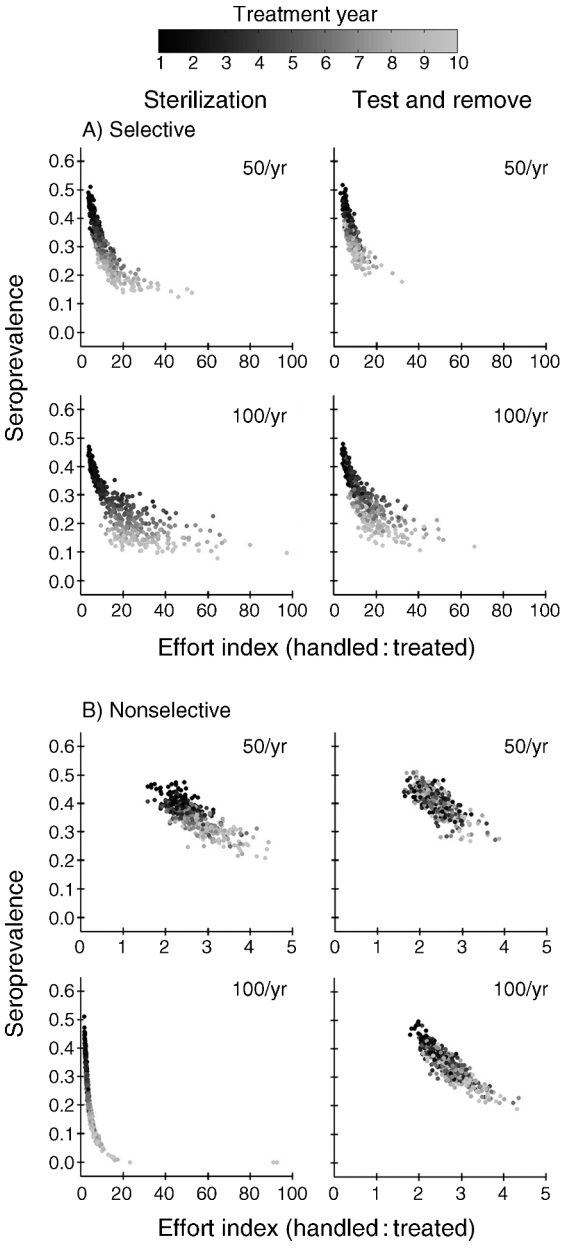

FIG. 4. Effort index (bison handled : treated) during the first decade of treatment vs. seroprevalence for (A) selective and (B) nonselective sterilization and test-and-remove at low (50 bison/yr) and high (100 bison/yr) objective treatment levels under low recrudescence. Grayscale intensity indicates the time component in years of consecutive treatment (1–10). Note that the *x*-axes vary.

focused on reporting the results for the first decade of treatment when ratios typically stayed below this level. This allowed for more meaningful comparisons of strategies, across treatment levels, and selectivity scenarios that might actually be applicable in field situations. Selective management under sterilization resulted in a seroprevalence of 20% or less during 13.5% (objective = 50 per year) and 41.3% (objective = 100 per year) of simulations during the first decade of management. Selective test-and-remove reached the same benchmark only <0.1% (objective = 50 per year) and 18.3% (objective = 100 per year) of simulation years. This larger reduction in seroprevalence with fewer available animals to treat during the first decade of treatment resulted in higher effort values for sterilization compared to test-and-remove, as well as a shorter duration of management years to reach a given effort level (Fig. 4). Nonselective treatment of seropositives significantly reduced the amount of effort required for both sterilization and test-and-remove across all objective levels (Fig. 4). The ability to frequently reach objective levels during the first decade of treatment using nonselective sterilization achieved the largest reductions in seroprevalence for the least amount of effort. The mean effort for simulation years with a seroprevalence of 20% was 27.9 handled/treated for selective and 4.1 handled/treated for nonselective sterilization treatments. Beyond the first decade of treatment, strategies that targeted seropositive bison had difficulty regardless of strategy or selectivity when seroprevalence dropped to <10%. Selective vaccination required low effort, with values fluctuating just above one as the majority of calves tested negative for brucellosis exposure. Under nonselective and mixed applications, vaccination had a constant value of 1 as individuals were targeted regardless of age and without a serological test (i.e., every captured individual was treated). It should be noted that test-and-remove and sterilization strategies can regain some of their effort expenditure when considering the amount of effort required for population management, but interactions between disease prevalence and population growth rate must also be considered.

Seroprevalence was highly correlated with population growth rate in the absence of sterilization (Fig. 5). Nonselective sterilization caused initial decreases in seroprevalence and population growth rate (Fig. 5). As time progressed, however, sterilization counterintuitively resulted in higher population growth rates because the concomitant reduction in seroprevalence also reduced the number of disease-induced abortions. (Fig. 5; Appendix B, Figs. B7–B8). Under the nonselective treatment of 100 bison per year, the mean peak in the proportion of sterilized bison ($\bar{x} = 0.28$, $\sigma = 0.02$) occurred between years 9 and 15 of consecutive treatment and led to eradication of the disease and the cessation of sterilization treatments. Thus, the highest population growth rates ($\lambda \approx 1.1$) occurred in simulations with aggressive sterilization, which resulted in disease eradication. Once treatments stopped all sterilized bison eventually died and population growth rates increased.

Many simulations showed rapid rebounds in seroprevalence after initial declines, a phenomenon we refer to as a ricochet (Fig. 6). These anomalies occurred in 9% of test-and-remove simulations and 4% of sterilization

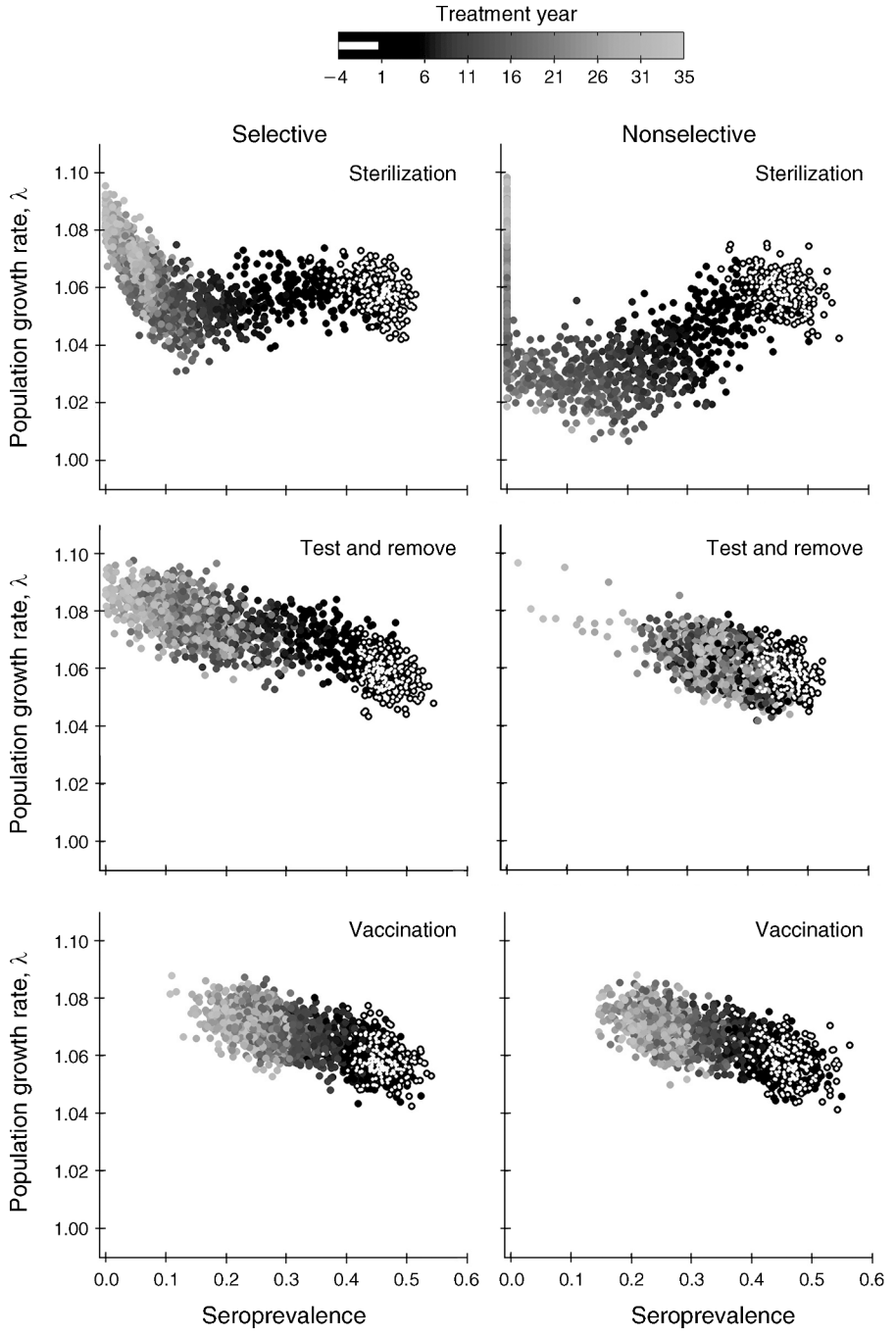

FIG. 5. Changes in population growth rate (λ) with reductions in seroprevalence for all management types with an objective treatment level of 75 bison/yr. The left-hand column shows selective applications, and the right-hand column shows nonselective (see Appendix B [Figs. B6 and B7] for additional objective levels). Grayscale intensity indicates the time component in years of consecutive treatment. Pretreatment years are indicated by open circles.

simulations, when recrudescence was low (Appendix B: Fig. B9). Under selective treatments, the frequency of simulations experiencing ricochet events decreased with increasing objective levels for both management types (test-and-remove, $\text{range}_{(50,75,100)} = 0.13–0.08$; sterilization, $\text{range}_{(50,75,100)} = 0.10–0.03$). Nonselective treatments also showed ricochets, with nonselective test-and-removal resulting in an increasing frequency of events with treatment level (test-and-remove, $\text{range}_{(50,75,100)} = 0.13–0.03$). The 100% eradication under sterilization at the objective levels of 75 and 100 bison per year resulted in zero ricochets (Appendix B: Fig. B9).

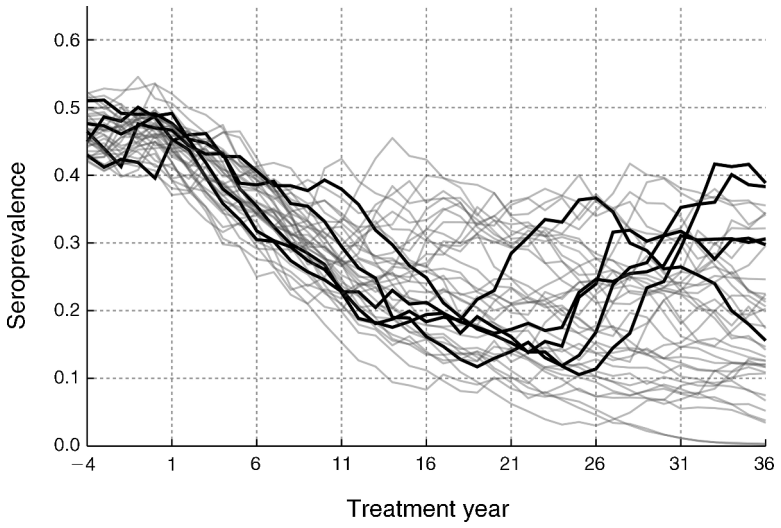

FIG. 6. Example of ricochet events in the times series for selective test-and-remove with an objective treatment level of 50 bison/yr. The bold black lines are examples of simulations experiencing ricochet events. Also apparent in the time series were early departures from the overall declining trend that are driven by the same dynamics as ricochets, but do not appear as rebounds because they occur early in the time series.

Model sensitivity

For all scenarios we ran identical simulations using high recrudescence parameter values (Appendix A: Table A1). High recrudescence primarily influenced the sterilization and test-and-remove strategies that focused on test-positive bison, with slight differences for vaccination (Appendix C: Fig. C1). In general, high recrudescence reduced the ability of high selectivity to decrease seroprevalence to very low levels (beyond 30% reduction in seroprevalence) and achieve eradications due to older individuals reverting to an infectious state from the recovered class and reducing the efficacy of focusing only on the pre-reproductive, test-positive class. The impact of recrudescence increased with increasing effect size (i.e., relative change in seroprevalence; Fig. 3; Appendix C: Fig. C2). The slower decreases in seroprevalence under high selectivity resulted in lower effort index values and slower decreases in the treated proportion of the objective levels (Appendix C: Figs. C3–C5). Higher recrudescence resulted in fewer ricochet events ($\bar{x}_{\text{test-and-remove}} = 1\%$, $\bar{x}_{\text{sterilization}} < 1\ \%$) compared to low recrudescence ($\bar{x}_{\text{test-and-remove}} = 9\%$, $\bar{x}_{\text{sterilization}} = 4\%$). Recrudescence had a relatively minor effect on vaccination, with slightly smaller decreases in seroprevalence under high recrudescence.

A Poisson contact distribution with the same mean number of contacts as the empirical negative binomial underrepresented the number of zero contacts and the rare but larger contact events when compared to the empirical data. We also extended the contact distribution toward more long-tailed negative binomial distributions with fewer zero contacts and a greater magnitude in the rare but large events (Appendix A: Table A1). Changes in the contact distribution required changes in the probability of recovery (γ) and or recrudescence (ω) to produce outcomes that were within the upper bound (0.60) of seroprevalence observed in Yellowstone bison. Although we fixed the probability of transmission given contact (φ) to be relatively high (see *Methods* section), in theory, this parameter could also be adjusted to account for alternate contact distributions (see *Discussion* section). We had difficulty finding parameter combinations that fit the empirical filters for high recrudescence with increasing heterogeneity in contacts and the modeled values used for high recrudescence under the two most heterogeneous distributions were slightly lower than preferred, but still at least two times the low recrudescence value.

The performance of vaccination was robust to the type of contact distribution across all management and selectivity levels, with the mean reduction in seroprevalence only varying a few prevalence points. Sterilization was sensitive to contact distribution, mostly in its ability to reduce seroprevalence at the objective level of 50 bison per year and to achieve true eradication. Sterilization appeared insensitive to the contact heterogeneity when 100 bison per year were nonselectively treated. Test-and-remove showed an increasing loss of power to reduce seroprevalence under selective application with increasing skew of the contact distribution. Objective levels of 50 and 75 bison per year were not able to move seroprevalence beyond vaccination levels and at the higher treatment levels reductions in seroprevalence were often overcome by an increased frequency of ricochets. However, when we reduced the variability of the contact distribution by modeling it as a Poisson distribution ricochet events no longer occurred regardless of the management strategy. Under the heaviest tailed distribu-

tion (contact distribution C; Appendix A: Fig. A1), test-and-remove of 100 bison per year experienced ricochet events during 50% of the simulations, and had a mean seroprevalence of 30% after 35 years of consecutive treatment. The robust performance of vaccination and sterilization compared to test-and-remove under different contact distributions suggests that the maintenance of herd immunity during disease mitigation, and the indirect protection these treated animals provide to susceptible individuals, became increasingly important with increased heterogeneity in the contact distribution. Under increased right-skew of alternate contact distributions, seroprevalence was more difficult to reduce and births were not offset by a concomitant reduction of abortions when management achieved objective levels for longer periods of time and more individuals were treated. Under such scenarios, there was a sustained decrease in the population growth rate for the entire simulation (Appendix C: Fig. C6).

Discussion

In most systems, the control of disease in wildlife populations remains difficult, if not impossible, due to logistical, financial, and sociological constraints. Managers are often faced with difficult decision between investing in cheap, weak management actions vs. more expensive but powerful approaches that are perhaps more cost effective in the long run (Keeling and Rohani 2008). Further complicating wildlife disease management is the tendency towards reductionist approaches and a focus on immediate results, however, as the ricochet events we observed in our model demonstrate, short-sighted assessments may be overly optimistic.

Brucellosis in the greater Yellowstone ecosystem is no exception to the abovementioned issues, but the biology of *B. abortus* does lend itself to more selective control strategies. In particular, males are assumed to play a negligible role in transmission and, if positive culture results are any indication of infectiousness, probably $<50\%$ of seropositive adult females are infectious. Further, the overriding importance of pregnancy and the reproductive system in the life cycle of *B. abortus* (Cheville et al. 1998) means pre-reproductive females, when infected, are unlikely to be infectious until they become pregnant. Thus, young reproductively active seropositive females are likely to drive brucellosis dynamics, but represent a small proportion of the population. As a result, sterilization focused on this population segment can be a highly effective strategy at relatively low treatment levels ($<5\%$ of the female population treated annually). However, because this treatment can be highly selective, it also requires more effort to find the appropriate individuals, which becomes more and more difficult as seroprevalence declines.

During the course of our simulations, we observed a dynamic that we refer to as a ricochet, which is likely to be generally applicable to other disease control and eradication programs. As seroprevalence and herd immunity declined due to test-and-remove or sterilization, a proportion of simulations had large subsequent increases in seroprevalence, sometimes increasing to pretreatment levels. We believe two factors drive this phenomenon: First, the well mixed nature of bison groups and long time intervals between contact and subsequent transmission allow contacts with infectious material (e.g., an abortion event within a group) to become widely dispersed by the time infected individuals are at risk of transmitting the disease. Second, there appears to be an interaction between herd immunity and transmission heterogeneity, which we model here as a negative binomial contact distribution. When seroprevalence is high, abortion events resulting in a large number of contacts result in less transmission than when the population is composed of a high proportion of susceptible individuals. Thus, the occurrence of super-spreading events are likely to increase as herd immunity decreases. Sterilization produced fewer ricochets than test-and-remove because treated individuals are not replaced in the population by susceptibles, but instead serve as dead-end hosts interfering with transmission and indirectly protecting some susceptible individuals from contacting infectious events. In a similar fashion, when seropositive treatments involve recovered individuals, sterilization does not result in their replacement with susceptible individuals (via birth) as is the case for test-and-remove. While the ability of sterilization to produce herd immunity effects is reduced as seropositives become increasing rare in the population, the opposite is true for vaccination. By treating susceptible individuals, vaccination provides individual protection and substantial herd immunity effects in the unprotected segment of the population while seroprevalence declines. For example, when relatively few individuals are responsible for most of the transmission, vaccination efficacy does not hinge on treating these key individuals as in the case of test-and-remove and sterilization; what matters is the proportion of vaccine protected individuals in the population at large.

The direct treatment of the infected class is clearly a powerful force in the reduction of disease transmission. However, treating infected individuals is complicated by diagnostics, which in the case of serology only provide information on exposure. We assessed the efficacy of using age and serology together through selective treatments to increase the potential of treating infectious individuals and how those treatments impact disease and population dynamics. Under selective applications, the power of treating pre-reproductive seropositives quickly reduces seroprevalence, but this reduces the influx of individuals entering the recovered class, thus reducing herd immunity. As management actions decrease the force of infection, the average age of infection increases (Anderson and May 1991). For selective management, the narrow focus on pre-reproductive bison that initially served as a strength changes to a weakness as the average age of infection slides beyond management's relatively

narrow field of view. Without a substantial herd immunity effect, transmission can proceed unchecked and prevalence levels rise accordingly. More sophisticated and flexible strategies that decrease selectivity as seroprevalence declines would provide more efficient disease mitigation in the long run.

Our simulations showed large variations in potential outcomes across all management strategies after 35 years of consecutive treatment, especially for strategies focusing on treating seropositive animals (Fig. 3). While the initial and short-term impacts of management on seroprevalence (<10 years) were often similar, they were not reliable indicators of long term trends (Fig. 6). Accordingly, optimistic views about reductions and/or eradication based solely on the initial years of management may not reflect the true trajectory of disease dynamics. It is important for readers to focus on the range of simulation outcomes when evaluating model results as this indicates both the best and worst case scenarios for a given strategy.

Reductions in brucellosis seroprevalence are likely to result in increases in population growth rate (Fig. 5; Fuller et al. 2007*a*). In the Yellowstone context, an increased growth rate will probably result in more bison leaving the park and increased boundary removals (Geremia et al. 2011). This may have far-reaching consequences because there is a positive relationship between the number of bison leaving the park and the overall population size (Cheville et al. 1998, Kilpatrick et al. 2009). Given that brucellosis eradication in the near future is unlikely (Bienen and Tabor 2006, Treanor et al. 2010), the costs of boundary management could potentially increase in the future if bison have higher population growth rates. Sterilization provides a means to impact both seroprevalence and population growth rate. Nonselective sterilization reduced population growth rate, but population growth rate did rebound and even exceeded pre-treatment levels if the disease was eradicated and/or treatments ceased. One potential approach for sterilization is in a mixed framework with vaccination, where it may counteract the shift from infectious abortions to healthy live births as disease prevalence declines. For example, under mixed vaccination and sterilization, ~5% sterilization level resulted in a sustained population growth rate when seroprevalence is reduced to the 15–25% range (Appendix B: Fig. B10). Achieving these minor levels of sterilization in the mixed context required a treatment across all ages, because focusing on only pre-reproductive females or calves failed to reach sterilization levels above 3%.

Our model shows that sterilization, when used as a means of preventing pregnancy in brucellosis-infected bison rather than for population control, can be a powerful management tool. Although the intention of sterilization is not population control, if not considered carefully, the potential exists for unintended and potentially catastrophic results such as sustained negative population growth ($\lambda < 1.0$) for prolonged periods. If sterilization does not treat enough infectious individuals, but instead treats mostly recovered animals, then the reduction in live births due to sterilization is not offset by a reduction in disease related reproductive failures, and sterilization's effects become additive instead of compensatory. We observed this tendency under the alternative contact distributions where a smaller number of individuals played a larger role in transmission. Under these conditions, finding and treating infectious individuals was more difficult and it took more cumulative treatments to reduce seroprevalence and λ reached a minimum of 0.985 when objective levels were 100 bison per year.

The high cost of treating seropositives as they become scarce in the population suggest that a more reasonable approach for sterilization and test-and-remove would be the application of these strategies for a limited duration during the onset of a management campaign, followed by alternative strategies that require less effort, such as vaccination. In this context, management may exploit the power of treating seropositives before the costs reach prohibitively high levels. For example, our model suggested that selectively treating 50 seropositive females per year for five years would result in a mean seroprevalence of 37% and a maximum handled to treated ratio of 7.4 for test-and-remove, and a mean 32% seroprevalence and maximum handled to treated ratio of 9.4 for sterilization.

In our simulations, mixed applications were dominated by vaccination because vaccination was applicable to a broader population segment, particularly as seroprevalence declined. Nonetheless, mixed treatments did show greater reductions in seroprevalence than vaccination alone (Appendix B: Fig. B4). If vaccination requires direct handling and serological testing of individuals, then treatment of seropositive animals becomes more attractive (by treating test positive individuals instead of just determining them unsuitable for vaccination).

Our results suggest that disease mitigation efforts can be successful with efforts that do not require treating all individuals and may be applicable to other systems than Yellowstone bison. However, for systems that require a fixed treatment area (e.g., elk feed grounds in Wyoming), management scenarios should account for greater group stability than what we have modeled for Yellowstone bison. In our modeling approach, grouping behavior and time between contact and subsequent infection (i.e., multiple seasons) supports the idea of using well mixed groups, though this assumption may not capture group dynamics of other systems.

We assumed that the probability of transmission given contact is relatively high given the massive number of bacteria expelled during reproductive failures and the attractant properties of fetal tissues in bison. While this concept is generally widespread in the brucellosis literature, the minimum effective dose required for successful transmission remains undetermined in bison (it has not been established unequivocally in cattle,

either). Additionally, many factors interact during disease transmission; including bacterial dose, route, temperature, and host stress and immune responses (Cheville et al. 1998). Therefore, it is possible that the level of transmission is lower than the relatively high levels of transmission given contact used in the model. However, indirectly, our empirical filters (seroprevalence, proportion of seropositives that are infected, and population growth rate) show that lowering of this parameter required concomitant changes in recovery (γ) and recrudescence (ω), which were not supported by the literature, for simulated disease dynamics to fall within the empirical range of data (see *Methods* section).

Wildlife contraception is a controversial topic among wildlife biologists, managers, and the general public, which may never be free from strident debate (Kirkpatrick 2007). We feel it is important to reiterate that sterilization in our model is used as a disease mitigation strategy and not a population control strategy. Models of sterilization for population control show that very high levels of coverage are typically needed (range 50–96%; Hobbs et al. 2000) and depend on population objectives (e.g., maintenance vs. reduction). For example, in white-tailed deer, Merrill et al. (2003) showed that to achieve a 60% reduction in four years, a 40% reduction in fertile females is needed each year. Our model indicates that disease reduction from sterilization can be achieved with substantially smaller levels of sterilization. Nevertheless, the lifetime effect of sterilization, history of periodic large-scale bison culls, and the long-lived nature of bison, warrants caution in using any strategy that has the potential for reducing population growth (λ) to ≤ 1 for any period of time.

Fertility control products have several potential side effects, such as extended breeding seasons, changes in life span, reduced genetic diversity, and alterations in social behavior and organization that should be considered prior to any management intervention (McShea et al. 1997, Heilmann et al. 1998, Powell 1999, Powers et al. 2007, Killian et al. 2008, Kirkpatrick and Turner 2008, Baker et al. 2009, Gionfriddo et al. 2009, Nuñez et al. 2009, Ransom et al. 2010). Although we have no hard data documenting these side effects in bison, nor are there likely to be rigorous studies of sterilization side effects in bison in the near future, these concerns are real, defensible, and worthy of further discussion. For now, these concerns and the intrusive human intervention required to implement sterilization likely limit the National Park Service's management discretion to employ sterilization given their mission and principles for managing biological resources (National Park Service Organic Act of 1916 and General Authorities Act of 1970; U.S. NPS 2006). However, we encourage scientists and policy makers to consider the entire suite of available disease management tools and creatively develop effective alternatives or combinations that also minimize long-term impacts to Yellowstone bison and their conservation.

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APPENDIX A

Model structure and parameters (*Ecological Archives* A021-133-A1).

APPENDIX B

Additional model results (*Ecological Archives* A021-133-A2).

APPENDIX C

Results of the model sensitivity analysis (*Ecological Archives* A021-133-A3).