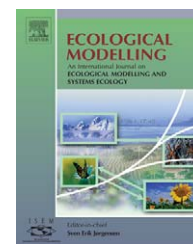


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Assessing vaccination as a control strategy in an ongoing epidemic: Bovine tuberculosis in African buffalo

Paul C. Cross^{a,*}, Wayne M. Getz^{b,c}

^a Northern Rocky Mountain Science Center, United States Geological Survey, 229 AJM Johnson Hall, Bozeman, MT 59717, United States

^b Department of Environmental Science, Policy and Management, 140 Mulford Hall #3114, University of California, Berkeley, CA 94720-3112, United States

^c Mammal Research Institute, Department of Zoology and Entomology, University of Pretoria, Pretoria 0002, South Africa

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ABSTRACT

Bovine tuberculosis (BTB) is an exotic disease invading the buffalo population (*Syncerus caffer*) of the Kruger National Park (KNP), South Africa. We used a sex and age-structured epidemiological model to assess the effectiveness of a vaccination program and define important research directions. The model allows for dispersal between a focal herd and background population and was parameterized with a combination of published data and analyses of over 130 radio-collared buffalo in the central region of the KNP. Radio-tracking data indicated that all sex and age categories move between mixed herds, and males over 8 years old had higher mortality and dispersal rates than any other sex or age category. In part due to the high dispersal rates of buffalo, sensitivity analyses indicate that disease prevalence in the background population accounts for the most variability in the BTB prevalence and quasi-eradication within the focal herd. Vaccination rate and the transmission coefficient were the second and third most important parameters of the sensitivity analyses. Further analyses of the model without dispersal suggest that the amount of vaccination necessary for quasi-eradication (i.e. prevalence < 5%) depends upon the duration that a vaccine grants protection. Vaccination programs are more efficient (i.e. fewer wasted doses) when they focus on younger individuals. However, even with a lifelong vaccine and a closed population, the model suggests that >70% of the calf population would have to be vaccinated every year to reduce the prevalence to less than 1%. If the half-life of the vaccine is less than 5 years, even vaccinating every calf for 50 years may not eradicate BTB. Thus, although vaccination provides a means of controlling BTB prevalence it should be combined with other control measures if eradication is the objective.

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1. Introduction

Bovine tuberculosis (BTB, *Mycobacterium bovis*), an airborne bacterial pathogen, is re-emerging in wildlife and livestock worldwide. In the Kruger National Park of South Africa, BTB is increasing in prevalence and moving northwards from its

introduction from cattle along the southern border of the KNP in the early 1960s (Bengis et al., 1996; Bengis, 1999; Rodwell et al., 2001). Buffalo are a reservoir host, maintaining the disease at high prevalence (over 60% in some herds), while predators such as lions and leopards appear to be spill-over hosts (Keet et al., 1996; Rodwell et al., 2000). BTB is a chronic and progres-

* Corresponding author. Tel.: +1 406 994 6908; fax: +1 406 994 6556.

E-mail address: pcross@usgs.gov (P.C. Cross).

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sive bacterial disease with a wide host range, and there is no evidence that animals recover from infection (Bengis, 1999). As in cattle, most buffalo are infected with BTB via aerosol transmission (Bengis, 1999). Vertical (intrauterine) and pseudo-vertical transmission (through infected milk) may occur but appear to be rare events (Bengis, 1999). The pathology of BTB in lions suggests that they acquire the disease by consuming infected buffalo (Keet et al., 1996), and it remains unclear how the effects of BTB, with its wide range of potential hosts, will ripple through the KNP ecosystem.

Due to the potential effects of BTB on buffalo and alternative host species, KNP managers would like to control or eradicate BTB via culling, vaccination, or some combination of the two. Previous modeling work on BTB in buffalo suggests that BTB may persist even when the buffalo population is reduced to low densities, making random culling, for the purpose of eradication, problematic (Rodwell, 2000). Thus, vaccination, or some combination of vaccination and culling, is a more attractive management option. Early action is likely to be the most effective, however there are many uncertainties surrounding the potential impacts (or lack thereof) of BTB on the buffalo population, the efficacy and duration of the vaccine in buffalo, and the logistic difficulties of a vaccination program. Here, we use an epidemiological model to tackle some of these questions surrounding management of the disease using the best available data. Analysis of the model provides the rapid answers required by managers and helps to focus further research projects.

Vaccination trials with Bacille Calmette-Guérin (BCG) and buffalo are currently underway in the KNP as the vaccine has been shown to give protection to cattle, deer, brushtail possums, ferrets, and badgers (for a review see Suazo et al., 2003). In cattle, BCG has been used in a number of trials and the amount of protection has varied widely (e.g. Francis, 1958; Berggren, 1977; Rodrigues et al., 1993; Colditz et al., 1994; Buddle et al., 1995c). More recent BCG vaccination trials in New Zealand have demonstrated up to 70% protection in cattle (Buddle et al., 1995c), data on the longevity of protection of the BCG vaccine, however, are non-existent in buffalo and limited in cattle (Berggren, 1977). Preliminary data from a captive study of African buffalo indicate that the BCG vaccine was not particularly effective, but the researchers believed this could have been due to the artificial conditions in the captive situation and are conducting further studies in a more natural context (De Klerk-Lorist, 2005). Here, we use an SEI (susceptible–exposed–infectious) epidemic model to assess the potential effectiveness of a buffalo vaccination program.

Several models of BTB in wildlife and cattle have been published previously (e.g. Benteil and Murray, 1993; Barlow et al., 1997; Smith et al., 2001b; Smith and Cheeseman, 2002; Shirley et al., 2003; Wilkinson et al., 2004), and a few studies have investigated the efficacy of different management strategies (e.g. Peterson et al., 1991a,b; White and Harris, 1995; Kao et al., 1997; Barlow et al., 1998). This study, however, is the first to assess the likely efficacy of a vaccination program for African buffalo. The effectiveness of control programs in African buffalo is likely to differ from other wildlife species and cattle for several reasons. First, African buffalo tend to live longer than other host species that are infected with BTB (e.g. badgers, possums, deer and cattle). Second, BTB appears to have

only minor effects upon the survival of buffalo (Rodwell et al., 2001). As a result, BTB can reach high prevalence (60–92%) in buffalo herds (Bengis, 1999; Rodwell et al., 2000; Jolles, 2004). In contrast, the prevalence of BTB in badgers and possums has tended to be less than 20% (Smith, 2001). Thus, the amount of vaccination necessary to control BTB in African buffalo is likely to be much higher than what would be expected from previous estimates on different host species. Here, we use mathematical modeling combined with field data to assess the likely success of a vaccination program in free-ranging populations of African buffalo. The sex and age structure of this model allows us to investigate how managers may focus control efforts in a large ungulate, and how this management may be affected by the movement patterns of different age and sex categories.

Mathematical models exist along a continuum from detailed data-based models used for predictions about specific systems (e.g. Wilkinson et al., 2004) to models intended to improve understanding of general processes (e.g. Cross et al., 2005b). We attempt to balance the specific and the general by using the limited data available to draw conclusions about the likely efficacy of a vaccination program, and the degree to which our conclusions depend on specific model parameters. Since there has been comparatively little research conducted on BTB in African buffalo we keep our model relatively simple, including a minimal amount of structure. In contrast, research on BTB in badgers and possums has been ongoing for many years, and, as a result, the corresponding modeling analyses can be much more specific (e.g. Anderson and Trehwella, 1985; Barlow, 1991; Smith, 2001). The data to construct and support this model of BTB in buffalo come from cross-sectional surveys in the KNP (Rodwell, 2000) and Hluhluwe-iMfolozi Park (Jolles, 2004), our ongoing longitudinal study in the KNP (Cross et al., 2004, 2005a), and what is understood about the biology of BTB in buffalo and cattle. Research and management strategies, however, may need to be implemented prior to the collection of additional data and a general model of an SEI disease in a long-lived and social host may help to frame the problem and guide management decisions prior to their implementation.

We present preliminary analyses of field data to estimate dispersal and survival rates using data on over 130 radio-collared buffalo from November 2000 to December 2003. These estimates are then supplemented with published information on cattle and buffalo. The model is then used to assess the potential efficacy of a vaccination program and highlight the importance of several model parameters. For the model, we assume that the vaccine protects individuals in any sex and age category completely, but that protection may wane over time. Even though an effective vaccine with these characteristics is not yet available, our model can be used to assess what elements are necessary for a successful vaccination program.

The technical part of this paper begins with a presentation of a discrete time SEI model. This model builds upon previous models of bovine tuberculosis in cattle and wildlife (e.g. Benteil and Murray, 1993; Ruxton, 1996; Barlow et al., 1997; Kao and Roberts, 1999; Smith et al., 2001a) by incorporating dispersal, vaccination, sex, and age structure. Next, we outline the parameter estimation procedures and conduct sensitivity analyses of the model to determine which parameters explain the most variability in disease prevalence and eradication. We

then further investigate the model in a single herd context (i.e. without dispersal to a background population). Finally, we assess the potential effectiveness of a vaccination program and whether it can be improved by focusing on different sex and age categories.

2. Methods

2.1. Simulation model

The model presented here is an age- and sex-class elaboration of a discrete time SEI epidemic model for a focal buffalo herd in contact with a background population. We use a 1-month time step to account for the annual reproduction and vaccination of buffalo and the within-year transmission dynamics of BTB. Let X , Y , Z and V represent the number of individuals respectively susceptible to infection, exposed but not yet infectious, infectious, and vaccinated, and let $N = X + Y + Z + V$ represent the total number of individuals. We assume that exposed individuals (Y) become infectious at a constant “incubation rate” γ . A proportion $\psi(t)$ of the population is vaccinated every June, and a constant proportion δ of the vaccinations fail in each month.

immigrate to as emigrate from our focal herd. Further, we assume a constant proportion of the immigrants are susceptible (p_x), exposed (p_y), infectious (p_z), and vaccinated (p_v) for the duration of each simulation. This would be equivalent to vaccinating a focal herd that is embedded in a background population that is either in equilibrium or being maintained at some reduced prevalence. The model can then be used to inform managers about the effects of reducing movement between the focal herd and background population as well as reducing the prevalence of infection in the background population.

To incorporate sex and age structure, let $j = 1, 2$ represent the sex (1 = male, 2 = female) and $i = 1, \dots, 18$ the age class. We assume that a smaller proportion (s^2) of infectious individuals (Z) survive each time period than healthy individuals and that the survival of calves depends upon the total population size. We control the relationship between annual and monthly time using the index r defined by the statement:

IF mod(t , 12) = 0, THEN $r = 1$ ELSE $r = 0$

Assuming events occur in the following order: vaccination (ψ), transmission (β), vaccine failure (δ) and disease incubation (γ), emigration and immigration (ϵ), and survival ($s_{i,j}$), the monthly model equations conforming to the above assumptions are

$$\begin{aligned}
 X_{i+r,j}(t+1) &= s_{i,j}(N(t)) \left((1 - \epsilon_{i,j}) \left(\left(1 - \frac{\beta \sum_{i=1}^{18} \sum_{j=1}^2 Z_{i,j}(t)}{N(t)^\theta} \right) (1 - \psi_{i,j}(t)) X_{i,j}(t) + \delta V_{i,j}(t) \right) + p_x I_{i,j}(t) \right), \\
 Y_{i+r,j}(t+1) &= s_{i,j}(N(t)) \left((1 - \epsilon_{i,j}) \left(\left(\frac{\beta \sum_{i=1}^{18} \sum_{j=1}^2 Z_{i,j}(t)}{N(t)^\theta} \right) (1 - \psi_{i,j}(t)) X_{i,j}(t) + (1 - \gamma) Y_{i,j}(t) \right) + p_y I_{i,j}(t) \right), \\
 Z_{i+r,j}(t+1) &= s'_{i,j}(N(t)) ((1 - \epsilon_{i,j}) (\gamma Y_{i,j}(t) + Z_{i,j}(t)) + p_z I_{i,j}(t)), \\
 V_{i+r,j}(t+1) &= s_{i,j}(N(t)) ((1 - \epsilon_{i,j}) (1 - \delta) (V_{i,j}(t) + \psi_{i,j}(t) X_{i,j}(t)) + p_v I_{i,j}(t)), \\
 I_{i,j}(t) &= \epsilon_{i,j} (X_{i,j}(t) + Y_{i,j}(t) + Z_{i,j}(t) + V_{i,j}(t))
 \end{aligned}$$

Currently available vaccines require the use of a helicopter to dart or drive the buffalo into pens prior to vaccination. With either method, an individual’s disease status is unknown prior to capture. Since the capture and handling of individuals represents the majority of the cost of vaccinating wildlife, the repeated capture of already vaccinated individuals will increase the cost of a vaccination program. We account for this logistic difficulty by allowing for repeat vaccinations as well as the vaccination of already infectious individuals. Thus one measure of the efficiency of a vaccination program is the percentage of individuals captured that are successfully vaccinated for the first time (i.e. the percentage of individuals not infected nor previously vaccinated). We compare management strategies based on the ratio of successful to total vaccinations, assuming that vaccination protects only susceptible individuals. Finally, the number of total vaccinations can be multiplied by the cost of capturing and handling animals to more accurately reflect the probable cost of vaccination program.

We assume that a fixed proportion ϵ of individuals emigrate from the focal herd to a pool of individuals outside the herd each month. We do not consider the herd structure or demographics of this background population, but assume that during each month the same number of individuals, I ,

Annual reproduction is handled through the following statement that implicitly assumes an equal sex ratio at birth: IF mod(t , 12) = 0 THEN for $j = 1$ or 2 , $X_{1,j}(t) = \sum_{i=1}^{18} (b_i/2) (X_{i,2}(t) + Y_{i,2}(t) + Z_{i,2}(t) + V_{i,2}(t))$, $Y_{1,j}(t) = 0$, $Z_{1,j}(t) = 0$, and $V_{1,j}(t) = 0$, where b_i is the expected number of offspring per female each calving cycle (approximated to be in January each year). We assume that reproduction is independent of adult sex ratio, which cannot be true in the limits where males or females are absent from in the population, but it is a reasonable assumption for the range of population sizes we investigate here. Following Rodwell et al. (2001) in the KNP, we assume that BTB does not affect fecundity, although Jolles (2004) showed some effect of BTB on the fecundity of young and old buffalo, but not prime-aged buffalo from 5 to 8 years old. Disease transmission in the model depends on $1/N^\theta$ (Anderson and May, 1991), which is frequency-dependent when $\theta = 1$ and density dependent when $\theta = 0$. Population size in this model is relatively constant, so that selecting $\theta = 0$ or 1 is essentially equivalent to rescaling the transmission coefficient β . Therefore, the value of θ is not critical to our analysis and simulations with $\theta = 0$ were similar to those where $\theta = 1$ (data not shown). For brevity, we present results only for the frequency-dependent case $\theta = 1$. If contact data were available for a range of population densities, however, one could explicitly incorporate this into the transmission function (Barlow, 2000).

The model incorporates density-dependent survival in the first age-class (0–1 year) because long-term studies of large herbivores suggest that survival of adults varies little compared to juveniles (Gaillard et al., 1998, but see Sinclair, 1977). Density-dependent juvenile survival is regulated by an abruptness parameter ϕ , a scaling parameter κ , and the maximum survival rate s_0 (Getz, 1996):

$$s_{i,j}(N(t)) = \frac{s_0}{1 + \left(\frac{N(t)}{\kappa}\right)^\phi}, \quad i = 1, \quad j = 1, 2$$

This form of density dependence results in a stable age structure and relatively constant herd size, which allowed us to investigate different vaccination strategies in the absence of large population fluctuations. Since we restrict analyses to a relatively stable population size, the form of density dependence is unlikely to play a major role in these simulations. We decreased the maximum survival rate of infectious calves by a constant α_0 , where $\alpha_0 < s_0$, to obtain the survival function:

$$s'_{i,j}(N(t)) = \frac{s_0 - \alpha_0}{1 + \left(\frac{N(t)}{\kappa}\right)^\phi}, \quad i = 1, \quad j = 1, 2$$

Finally, we assumed that adult survival is constant over time, but depended upon the age, sex, and disease status of the animal, whereby the survival of infectious individuals was reduced by α_1 . We assumed that all buffalo in the 18th age-class died at the end of each year.

2.2. Parameter estimation

We based estimates of buffalo survival and dispersal on preliminary analyses of over 130 radio-collared buffalo from ongoing research in the central region of the KNP (Caron et al., 2003; Cross et al., 2004, 2005a). Depending upon the amount of herd fragmentation, the study area contained 4–12 buffalo herds and roughly 3000 buffalo. The majority of individuals were collared in four helicopter sessions: November 2000 ($N=6$), April 2001 ($N=27$), August 2001 ($N=51$) and November 2001 ($N=12$), while the remaining individuals were darted from ground vehicles throughout the study period. Animals were placed into age classes using incisor eruption patterns for those individuals under 5 years old (Pienaar, 1969; Grimsdell, 1973; Sinclair, 1977). For those animals over 5 years we used horn development and wear to subjectively place individuals into two categories: 5–7 years and 8+ years. We re-sighted collared individuals, on foot and from vehicles, approximately 2–3 times per week throughout the study period. If an individual was missing for over 1 month we relocated them from fixed-wing aircraft. We tested buffalo for BTB using a modified gamma-interferon (IFNg) BOVIGAM™ assay (Wood and Jones, 2001), which has similar sensitivity (82–100%) and specificity (~99%) to the intradermal skin test (Wood and Jones, 2001; Grobler et al., 2002; De Klerk-Lorist, 2005). Negative individuals were retested at 6- or 12-month intervals.

2.2.1. Survival

We assumed that calf survival ($s_{1,j}$) was density dependent and the maximum possible calf survival (s_0) was one (see above). Survival estimates for the other sex and age categories were estimated from field data with known-fate models in pro-

gram MARK using BTB-status, age, and gender as individual covariates (White and Burnham, 1999). The dataset consisted of 132 radio-collared buffalo from May 2001 to November 2003. Twenty-two buffalo were BTB-positive on the first test. Thirteen animals that converted from BTB-negative to positive were reclassified as positive individuals at the time of their first positive test. We assumed buffalo were BTB-negative if they were a multiple, equal, or avian reactor on the gamma-interferon test. For model selection of the survival data, we used AICc, which is a modified version of Akaike's Information Criterion (AIC) that corrects for small sample sizes relative to the number of parameters (Burnham and Anderson, 2002). The AIC approach is a method of comparing the goodness-of-fit of nested and non-nested models and discourages the use of models with too many parameters that overfit the data. The minimum and maximum values shown in Table 1 are the 95% confidence intervals for each parameter using the delta method (White and Burnham, 1999).

2.2.2. Dispersal (ϵ)

Previous studies suggest that only adult males move between herds (Sinclair, 1977; Prins, 1996). Using radio-tracking data of 120 buffalo in four herds from May 2001 to December 2003, we estimated the movement rate of buffalo between a focal herd and background population. We found lower cohesion amongst buffalo herds of the KNP than past studies (Cross et al., 2005a). At the start of the study, the study area appeared to contain four herds that separated and re-fused over time. Three of those herds fragmented and fused with herds in other areas of the KNP, thus making it difficult to define a dispersal event because the herd "dispersed" as a unit. As a minimum estimate of dispersal, we used the individuals in the remaining cohesive herd to estimate the probability of an individual moving from a focal herd to other herds in the background population. Individuals were assigned a value of zero or one respectively for every month they were present in the focal herd and either dispersed to another herd or remained in the focal herd. These data were then used in logistic regression analyses with sex and age as covariates. We excluded those dispersal events that lasted for less than 1 week because short duration events are unlikely to result in many disease transmission events. Animals were grouped into the following age categories: 1–2, 3–4, 5–7, and 8+ years old.

2.2.3. Disease transmission (β)

The transmission coefficient was estimated by fitting the model to the observed 1998 BTB prevalence values for the KNP (Rodwell et al., 2000). The model was parameterized with the baseline values in Table 1 and started with a disease prevalence of either 0.04 or 0.29 to correspond to the prevalence of BTB in the central and southern regions of the KNP in 1991. The initial population size was 250, to match the average herd size of the KNP (Whyte, unpublished data), and distributed among age classes to correspond to the stable age distribution predicted by the demographic component of the model. The model was run for 7 years and β was adjusted to minimize the sum of squared residuals between the predicted and observed prevalence in 1998. Transmission coefficient values that resulted in predicted 1998 prevalence values within the empirical 95% confidence intervals for the south and central

Table 1 – Parameter estimates used in the buffalo vaccination model

Parameter	Symbol	Minimum	Baseline	Maximum	Source
Annual buffalo survival					
Maximum calf survival	$S_{1,1-2}$	0.95	1.00	1.00	1
Young males	$S_{2-8,1}$	0.74	0.84	0.90	1
Old males	$S_{9-18,1}$	0.20	0.59	0.86	1
Young females	$S_{2-8,2}$	0.83	0.95	0.99	1
Old females	$S_{9-18,2}$	0.35	0.86	0.98	1
Scaling parameter	κ	–	400	–	See text
Abruptness parameter	ϕ	2	4	6	2
Annual buffalo reproduction					
Cows 3–4	r_3	–	0.51	–	3
Cows 4–5	r_4	–	0.64	–	3
Cows 5+	r_{5+}	–	0.68	–	3
Monthly dispersal					
Immature males	$\varepsilon_{1-6,1}$	0.01	0.02	0.04	1
Mature males	$\varepsilon_{7-9,1}$	0.24	0.09	0.03	1
Old males	$\varepsilon_{10+,1}$	0.45	0.26	0.13	1
Females	$\varepsilon_{1+,2}$	0.04	0.02	0.01	1
Monthly disease parameters					
Transmission coefficient	β	0.034	0.043	0.053	1
Incubation rate	γ	0.056	0.21	1	4
Reduction in maximum juvenile survival	α_0	0	0.0043	0.0084	5
Reduction in adult survival	α_1	0	0.0043	0.0084	5
Transmission exponent	θ	0	–	1	See text
Vaccination rate	ψ	0	–	1	See text
Vaccine failure rate	δ	0	–	0.056	6
Background prevalence	p_z	0	–	0.7	See text

1: this study; 2: Getz (1996); 3: Funston (1999); 4: Neill et al. (1991) and De Vos et al. (2001); 5: Rodwell et al. (2001), Caron et al. (2003), and Jolles (2004); 6: unknown, but see Berggren (1977).

regions were used to establish the minimum and maximum values in Table 1. Simulations assumed a closed population and no vaccination. Data from the northern region of the KNP were not used to parameterize β because no BTB-positive individuals were sampled in that area prior to 1998.

2.2.4. Other model parameters

The pathology of BTB in buffalo and cattle suggests that BTB lesions are not encapsulated by the immune system and individuals are probably infectious within a few months of infection (De Vos et al., 2001). Neill et al. (1991) estimated the latency period of BTB in cattle to be 87 days. De Klerk-Lorist, however found only 3 of 14 infected African buffalo with macroscopic lesions in the lungs within 34 weeks, and no individuals had macroscopic lesions in the lungs within 22 weeks of infection (De Klerk-Lorist, 2005). These data are not sufficient to estimate an average latency period, but they suggest that the time between infection and infectiousness may be longer in African buffalo than for cattle. We chose a baseline monthly incubation rate γ of 0.21, which relates to a mean incubation period of roughly 5 months, or a half-life of 87 days (i.e. half of infected individuals become infectious within 87 days). However, due to the limited data available on incubation rate, γ , we chose a wide range of 0.056 to one for the sensitivity analyses. Since ϕ is probably between two and six (see discussion in Getz, 1996), we used a value of four and adjusted κ to yield a stable herd size of around 250 individuals. Given the limited data available on the duration of vaccine protection in buffalo and the indication in Berggren (1977) and Francis (1958)

that protection wanes in vaccinated cattle between one and 5 years, we explored a wide range of vaccine failure rates from lifelong protection (i.e. $\delta=0$) to a half-life of 1 year.

2.3. Sensitivity analyses

Sensitivity analyses were conducted using Monte Carlo methods to assess the relative effects of several model parameters. Specifically, 10,000 random parameter sets were created by choosing ψ , δ , β , γ , $\varepsilon_{i,j}$, p_z , $S_{i,j}$, α_0 and α_1 from uniform distributions bounded by the minimum and maximum values shown in Table 1. We assumed that the vaccine was 100% protective for this analysis. Each parameter set was used to run the deterministic model once. The prevalence at year 50 was recorded for each run and used as the dependent variable in multiple linear regressions where model parameters were the explanatory variables (Wisdom and Mills, 1997; Wisdom et al., 2000; Cross and Beissinger, 2001). To facilitate comparisons between parameters measured on different scales all model parameters were transformed to percentage difference from the mean (i.e. $(x_i - \bar{x})/\bar{x}$, where x_i is the value of the model parameter on run i and \bar{x} is the mean) prior to statistical analysis. Subsampling this dataset and evaluation of standard errors revealed that 10,000 runs were sufficient to solidify the ranking hierarchy of the top six model parameters in the statistical analyses. The other eight parameters in the sensitivity analysis explained little variability in either disease prevalence or quasi-eradication, had large standard errors, and were omitted from Table 2.

Table 2 – Logistic and linear regression sensitivity analysis of 10,000 runs of the vaccination model using parameter values chosen from uniform distributions

Model parameter	Variable	Linear regression ^a		Logistic regression ^a	
		Coefficient	b/S.E. ^b	Coefficient	b/S.E. ^b
Background prevalence	p_z	0.222	476.5	–97.8	–13.0
Vaccination	ψ	–0.036	–77.1	3.0	9.3
Transmission coefficient	β	0.138	64.8	–16.8	–9.6
Reduction in adult survival	α_1	–0.019	–39.4	2.1	7.0
Female and juvenile dispersal	$\epsilon_{1-5,1,1+,2}$	0.026	32.7	3.0	6.2
Vaccine failure	δ	0.013	27.1	–1.0	–4.1

All parameters were transformed to % change from the mean and only the six most important variables are shown.

^a Multiple linear and logistic regressions with year 50 disease prevalence or eradication as the dependent variable, respectively.

^b Standardized coefficients were divided by the standard error to standardize measurements and yield a comparative measure of importance.

Model parameters were ranked according to the magnitude of their standardized coefficients (i.e. the regression coefficient divided by its standard error), which is a unitless quantity expressing the unique contribution of that variable scaled by the estimation uncertainty (Selvin, 1995). Model parameters that are good predictors of disease prevalence may be different from those that are good predictors of disease eradication. Logistic regression was used to identify the latter parameters (McCarthy et al., 1995; Cross and Beissinger, 2001). For the logistic regression analysis, disease prevalence at year 50 was converted to a binary variable of disease persistence or eradication. We used a prevalence of 5% as the quasi-eradication threshold because very few parameter sets resulted in quasi-eradication at lower threshold values making maximum likelihood estimation difficult in the logistic regression analysis. As in the linear regression analysis, each model parameter was transformed to percentage difference from the mean and individually used to predict disease eradication at year 50. All simulations started with 250 individuals in a stable-age distribution and an initial prevalence of 0.05, evenly distributed amongst all sex- and age-classes. The epidemiological model was coded in Matlab 5.3 (Mathsoft™) and statistical analyses were conducted using S-Plus 6 (Insightful Corp., 2001).

3. Results

3.1. Field data parameter estimates

Our survival data indicated that males and individuals over 8 years old had lower survival rates than females and those under 8 years old (Table 1). Age category (1–7 versus 8+) and gender were statistically significant explanatory variables in likelihood ratio tests (LRT) where we included one variable at a time ($p=0.004$ and 0.001 , respectively; $d.f. = 1$) and were supported in AICc analyses. There was little statistical support for the inclusion of more refined age categories using either AIC or LRT methods. Our analyses did not indicate any additional mortality amongst the 35 BTB-positive animals ($d.f. = 1, p=0.19$). Even though this is based on only the first 2 years of data, this result, in combination with previous cross-sectional analyses, suggests that the annual disease induced mortality associated with BTB is probably between 0% and 10% (Rodwell et al., 2000; Jolles, 2004). Statistical model comparisons using AICc values and sex, age (1–7 years, 8+), and

BTB-status as explanatory variables indicated that the additive sex + age model provided the best fit to the survival data. A sex × age model was the only other model that appeared to be supported by the data ($\Delta AICc = 0.869$). Using the sex + age model we estimated the survival rates shown in Table 1.

In contrast to previous studies of buffalo, we found that all sex and age groups moved between herds, albeit adult males moved between herds more frequently than young males and females (Table 1, Fig. 1). Logistic regression analyses indicated a significant age × sex interaction ($p=0.02$, $d.f. = 3$, deviance=9.88) whereby males over 8 years old were more likely to disperse (Table 1, Fig. 1). Due to the similar dispersal rates of females and juvenile males we aggregated these sex and age categories and reran the logistic model before calculating the dispersal rates in Table 1.

3.2. Sensitivity analyses

Sensitivity analyses of this model around the baseline set of parameter values indicate that for the model and parameter space presented, disease prevalence in the background population, p_z , is the primary factor determining the BTB prevalence in the focal herd (Table 2, $r^2=0.95$). Vaccination rate ψ and the transmission coefficient β were the second and

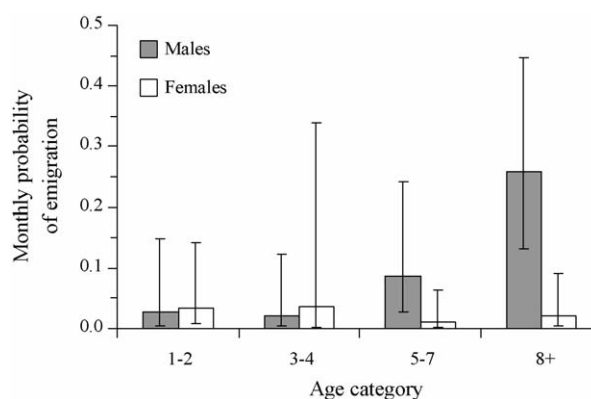


Fig. 1 – Buffalo emigration rates between a focal herd and the background population varied by sex and age in the central region of the Kruger National Park. Estimates were based on logistic regression analyses of the probability of dispersal per month. Bars represent the 95% confidence intervals.

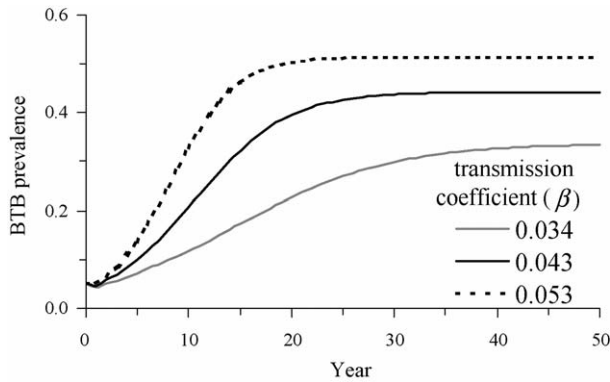


Fig. 2 – Predicted BTB prevalence plotted as a function of time using the upper, lower and baseline values of the transmission coefficient ($\beta = 0.034, 0.043, 0.053$). Simulations assume a closed population and no vaccination effort.

third parameters in the ranking hierarchy, while survival rates explained very little variability in BTB prevalence or eradication. There were few differences in the ranking of the top five parameters between the linear and logistic regression results indicating that parameters that regulate prevalence also determine the probability of eradication.

3.3. Model results without dispersal

To assess the effects of other variables we analyzed the model in the context of a single herd without dispersal (such as a cattle herd or small reserve). Using the baseline values in Table 1, the model predicts that BTB should reach an asymptotic prevalence of ~ 0.44 in a herd of ~ 250 individuals, and as would be expected of a chronic disease without recovery, the model does not exhibit any cyclical behavior (Fig. 2). Optimal vaccine strategies depend on the distribution of vaccinations to different sex and age categories and the duration of vaccine protection. Assuming that the vaccine grants lifelong protection, the model suggests that control programs should focus upon younger individuals. In particular, focusing the control strategy on younger individuals produces a higher ratio of successful to total vaccinations (i.e. less wasted vaccinations) than vaccinating individuals in proportion to the age structure of the population (Fig. 3). As vaccine duration decreases, however, the advantages of vaccinating juveniles decreases and the lines in Fig. 3 approach the efficiency of the calf-only vaccination strategy. In other words, when the vaccine lasts for shorter amounts of time there are fewer redundant vaccinations of older individuals. Few differences exist between the efficacy of male or female vaccination programs of a focal herd without dispersal (Fig. 3). However, in model simulations with dispersal (data not shown) vaccination programs were more effective if they focused on females because vaccinations of dispersing males were, in effect, wasted with respect to reducing prevalence in the focal herd.

In the best-case scenario of a 100% effective vaccine that provides life-long protection, a vaccination program focusing upon calves would require the vaccination of around 70% of

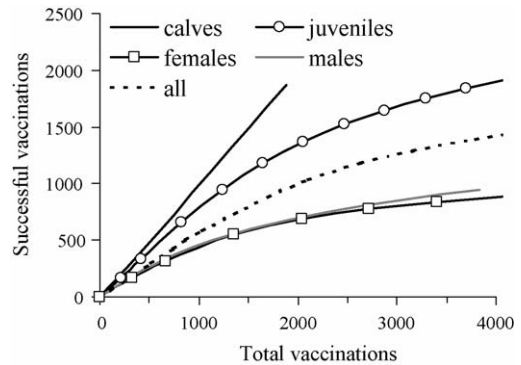


Fig. 3 – The number of successful vaccinations for the indicated vaccination strategies (i.e. focusing on calves, juveniles, males, females or the entire population) plotted as a function of the total vaccinations in a herd by year 50. “Successful” is defined as the vaccination of uninfected and previously unvaccinated individuals. “All” indicates a management strategy that vaccinates all individuals in proportion to their abundance in the population. Simulations assume a closed population and lifelong vaccine protection.

the calves every year to eradicate (i.e. prevalence $< 1\%$) BTB by year 50 (Fig. 4a). A program focused on the entire population would require a vaccination rate of less than 30% for eradication (Fig. 4a). However, 70% of the calf population translates into ~ 1300 vaccinations over a 50-year-period; whereas, 30% of the total population translates into ~ 3100 vaccinations over the same time period in a herd of approximately 250 individuals. Thus a calf-only policy requires higher coverage of that age-class but fewer vaccinations in total. This is not surprising given that calves are approximately 16% of the total population and we have assumed lifelong vaccine protection. If vaccination programs operate by herding many individuals at a time into holding pens rather than darting individuals by helicopter the financial implications of wasting vaccine doses on already vaccinated or infected individuals are less severe. Further, vaccinating a percentage of all age-groups will control the disease more quickly than vaccinating the same percentage of calves.

Given that vaccination rate ψ and vaccine failure rate (also expressible in terms of the half-life of the vaccine) δ are two parameters that may be altered by managers or scientists, we calculated BTB prevalence at year 50 for different combinations of these parameters and calf-only vaccination program (Fig. 5). Model results suggest that if 70% of the calf population is vaccinated every year BTB would may be eradicated by year 50 assuming the vaccine granted lifelong protection and no migration between the focal herd and background population. If the half-life of the vaccine was less than 5 years, however, a vaccination program is unlikely to eradicate the disease by year 50 with a calf-only vaccination program (Fig. 5). Even when all age and sex categories are vaccinated, however, over 60% of the population may need to be vaccinated every year to eradicate the disease by year 50 (data not shown).

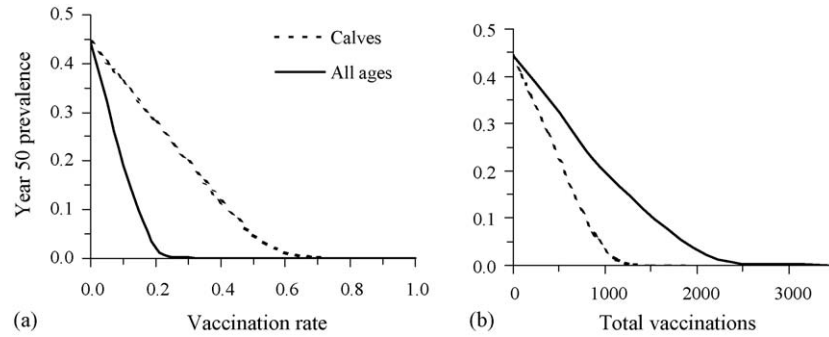


Fig. 4 – Prevalence of BTB at year 50 plotted as a function of: (a) vaccination rate and (b) cumulative vaccinations to demonstrate the importance of focusing vaccination effort on calves. Simulations assume a closed population, vaccination in proportion to abundance in the focal population, and lifelong vaccine protection.

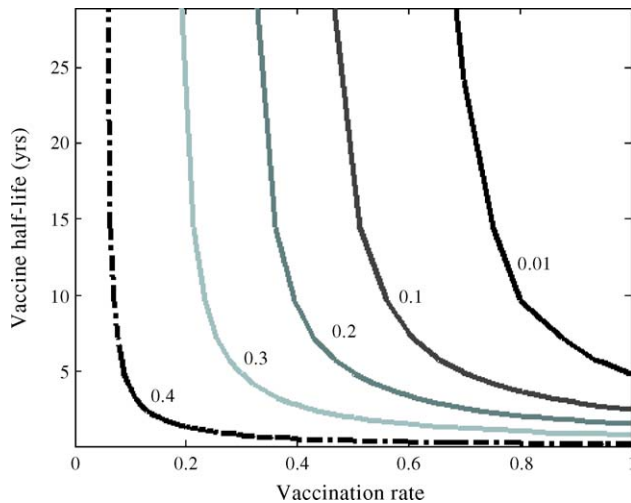


Fig. 5 – Prevalence isopleths at year 50 as a function of vaccination rate and vaccine half-life. Simulations assume a closed population and an annual calf-only vaccination program. Vaccine half-life refers to the amount of time before half of the vaccinated individuals are susceptible again.

4. Discussion

The management issues surrounding bovine tuberculosis in the Kruger National Park of South Africa are typical of many invasive species and emerging infectious diseases. Immediate actions are more likely to be effective, but limited data are available upon which to base management and research decisions. We used field data to bound the range of possible parameter values and simulated an SEI disease model to assess the importance of different model parameters and the effectiveness of vaccination as a control strategy. Our results, based upon the first analysis of a dynamic epidemiological model of BTB in a buffalo population, indicate that vaccination alone is unlikely to be an effective management tool to eradicate BTB. The literature on modeling BTB in other species is extensive and conclusions vary, but, in general, our con-

clusions about the utility of vaccination is in contrast with more encouraging modeling studies on vaccination of BTB in possums, badgers, and cattle (Barlow, 1991; White and Harris, 1995; Roberts, 1996; Kao et al., 1997; Tuytens and MacDonald, 1998; Smith, 2001; Smith and Cheeseman, 2002; Wilkinson et al., 2004). This difference may be due to the high prevalence of BTB in African buffalo (>50%; Rodwell et al., 2000) compared to <20% for badgers and possums (Krebs et al., 1997; Woodroffe et al., 1999; Coleman and Cooke, 2001). Our results and conclusions, however, are similar to those Peterson et al. (1991a), who showed that vaccination alone was unlikely to control brucellosis in bison over a 20 years timeframe.

Our model predicts that BTB should reach an asymptotic prevalence of around 44% assuming a closed population and a relatively constant herd size of 250 individuals (Fig. 2). Data from one herd in the southeastern corner of the KNP suggests that this estimate of asymptotic prevalence may be low. The Mpanamana herd of the KNP had a stable prevalence of 67% in 1992 and 1996 (De Vos et al., 2001). In addition, Jolles (2004) estimated the asymptotic BTB prevalence to be 53% (95% CI = [49–58%]) in Hluhluwe-iMfolozi Park. Additional data on BTB prevalence and transmission rates would help discern whether our parameter estimates or model structure should be modified to match the higher prevalence seen in these two herds. If this is the case, then our model results may represent optimistic estimates of the vaccination effort necessary to control and eradicate BTB.

Assuming frequency-dependent transmission and a vaccine that is equally effective and protective across all sex- and age-classes, vaccination programs will be most efficient on a per capture basis in reducing prevalence in the focal population if they focus on calves (Figs. 3 and 4). Vaccination of a proportion of all age and sex categories will reduce prevalence more than vaccinating the same proportion of calves, but at the cost of capturing more individuals. Younger individuals are unlikely to be infected or previously vaccinated, thus increasing the ratio of successful to total vaccinations (Fig. 3). Also, younger individuals will, on average, remain longer in the population than older individuals. Therefore, vaccinated calves will contribute more to herd immunity than vaccinated adults. The BCG vaccine has been the most comprehensively tested BTB vaccine in wildlife and cattle (e.g. Ellwood and

Waddington, 1972; Waddington and Ellwood, 1972; Berggren, 1977; Aldwell et al., 1995; Buddle et al., 1995a,b,c, 1997; De Klerk-Lorist, 2005). Due to the fact that the efficacy of the BCG vaccine may be reduced by prior exposure to environmental mycobacteria (Buddle et al., 1995a; Fine, 1998), BCG vaccination may also be most effective in the younger age groups. Thus, the vaccination of younger rather than older individuals is supported for both biological and mathematical reasons (Fig. 3).

Even in the best-case scenario of a 100% effective vaccine with lifelong protection, a management program focused on calves would need to vaccinate around 70% of calves every year to eradicate BTB by year 50 (Fig. 4a). In a herd of 250 buffalo this translates to around 1500 vaccinations over a 50-year-period (Fig. 4b). Our predictions may be overly optimistic since we assumed that all vaccinated individuals were protected against infection and our estimated asymptotic herd prevalence may be lower than that observed in the field. Given that: (1) the current BCG vaccine is very unlikely to be 100% effective in buffalo, (2) that protection probably wanes over time (Berggren, 1977; Buddle et al., 2000), (3) that drug and labor costs for vaccinating a buffalo are over US\$ 100 per individual, and (4) a high percentage of individuals must be vaccinated to eradicate the disease, the eradication of BTB via vaccination alone is probably not an effective management strategy. Vaccination may be useful to control BTB at lower prevalence levels, but then the question arises as to whether the cost of an indefinite control program outweighs the benefit in reduced prevalence. At this point, we cannot answer this question because it rests upon the effect of BTB on lion populations and the relationship between the prevalence of BTB in lions and buffaloes. Additional work on the interaction of lions, buffaloes, and BTB, and the degree to which lions select for BTB-positive individuals would be enlightening. Further, additional modeling work is necessary to assess the potential effectiveness of vaccination, in combination with other control measures such as a test-and-remove program, in a spatially explicit context. These analyses, however, should account for the potential difficulties that may arise if vaccinated individuals cannot be differentiated from infected individuals.

Sensitivity analyses suggest that disease incubation (γ) and buffalo survival rates were relatively unimportant model parameters (i.e. they explained very little variability in the prevalence or probability of eradication of BTB). Surprisingly, the dispersal rate was also relatively unimportant in the sensitivity analyses. The importance of dispersal, however, is reflected in the importance of the background prevalence, whereby higher dispersal rates increase the importance of the background prevalence (data not shown). Vaccination rate and the transmission coefficient are a distant second and third in the ranking hierarchy compared to the disease prevalence in the background population (Table 2). This result is obvious in hindsight given the model structure presented here and the high dispersal rates of buffalo in the KNP (Table 1, Fig. 1). It is important to note, however, that other studies of African buffalo indicate a more stable herd structure with less movement between herds in other areas (Sinclair, 1977; Prins, 1996). If these differences reflect real differences rather than an artifact of sampling intensity it would suggest that disease control is likely to be more effective in these less mobile populations.

We parameterized the epidemiological model using previously published parameter estimates as well as data from a longitudinal study of radio-collared individuals in the central region of the KNP. The dispersal and survival rate estimates presented here are the first estimates based upon longitudinal studies of known radio-collared individuals. Previous estimates were based upon cross-sectional life-table analyses and/or a few known, but unmarked individuals (Sinclair, 1977; Prins, 1996; Jolles, 2004; Jolles et al., 2005). Analysis of the longitudinal dataset of known individuals indicated that dispersal rate varied by sex and age, whereby males over 8 years old were the most likely to disperse from the focal herd (Table 1, Fig. 1). In contrast to previous studies, we found females and juvenile males also moved between mixed herds via splinter groups when herds split and later fused with other herds (Cross et al., 2004, 2005a). We began the study with four herds in the study area. Since 2001 these four herds have splintered into as many as 13 herds and only one of the original herds remained as a cohesive unit within the study region. As a result it is difficult to define dispersal events when the herd itself is changing. We used the one cohesive herd to estimate dispersal rates, which, given the fluid and mobile nature of the other herds, should be seen as minimum estimates and highlights the importance of developing spatial models of disease spread.

Survival analyses indicated that survival was a function of both age and sex. Age categories could be collapsed to 1–7 years versus 8+ years and females survived better than males (Table 1). Comparing models, both the additive (sex + age) and interactive (sex \times age) survival models were supported by the data based upon AIC values and likelihood ratio tests. We did not find any increased mortality of BTB-positive individuals during the first 2 years of the study. Previous research by Rodwell et al. (2001), Jolles (2004), and Caron et al. (2003) suggests that the additional mortality due to BTB infection is around 11% or less. With our sample of 35 BTB-positive and 97 BTB-negative individuals, we would be unlikely to detect small differences in survival rates in a 2-year timeframe. The low mortality rate of infected individuals and the lack of any known recovery suggest that buffalo will maintain BTB at high levels (Fig. 2). This conclusion, in combination with the difficulty of eradicating this disease with a vaccination or culling program, and the ability of BTB to spill-over into other hosts (Bengis et al., 1996) presents a worrying scenario. Since lions are the dominant predator of adult buffalo, and BTB can infect lions via the gastrointestinal tract (Keet et al., 1996), the largest effects of BTB may be in altering the competitive dynamics of the large predator guild in the KNP.

The model presented here is based upon best empirical data currently available and provides an objective view of the likely effectiveness of a vaccination strategy as well as highlights important research and management issues. The importance of the background population in the sensitivity analysis suggests that managers should view herds, or parks, as open systems and incorporate the surrounding populations into their control strategies, and the degree to which such invasions must be controlled depends on the background prevalence of the disease. Further, researchers should focus on spatial disease models to incorporate individuals' movement patterns. The inclusion of spatial complexity into our model, and more data on transmission rates and the inter-herd move-

ment patterns of individuals are needed to assess the likely efficacy of a combined vaccination and selective removal of infected individuals in containing the spread of BTB in African buffalo. Nonetheless, the model presented here suggests that even in the best case scenario, vaccination alone is unlikely to be an effective control strategy for BTB in buffalo, and thus research and managers should focus on other possible methods to control the spread of this exotic disease.

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