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Running Head: *Bovine tuberculosis vaccination*

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

Paul C. Cross<sup>a,b</sup>, Wayne M. Getz<sup>a,b</sup>

<sup>a</sup> *Department of Environmental Science, Policy and Management, 140 Mulford Hall #3114,  
University of California, Berkeley, CA 94720-3112, United States*

<sup>b</sup> *Mammal Research Institute, Department of Zoology and Entomology, University of Pretoria,  
Pretoria 0002, South Africa*

**Correspondence:** Paul Cross, phone: +1-510-643-3918; fax: +1-510-642-7428, E-mail:  
pcross@nature.berkeley.edu

1 **Abstract**

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

22 **Key words: *Mycobacterium bovis*, African buffalo, disease modeling, dispersal, and**  
23 **vaccination**

## 1 **1. Introduction**

2

3 Bovine tuberculosis (BTB, *Mycobacterium bovis*), an airborne bacterial pathogen, is re-emerging  
4 in wildlife and livestock worldwide. In the Kruger National Park of South Africa, BTB is  
5 increasing in prevalence and moving northwards from its introduction from cattle along the  
6 southern border of the KNP in the early 1960s (Bengis et al., 1996; Bengis, 1999; Rodwell et al.,  
7 2001). Buffalo are a reservoir host, maintaining the disease at high prevalence (over 60% in  
8 some herds), while predators such as lions and leopards appear to be spill-over hosts (Keet et al.,  
9 1996; Rodwell et al., 2000). BTB is a chronic and progressive bacterial disease with a wide host  
10 range, and there is no evidence that animals recover from infection (Bengis, 1999). As in cattle,  
11 most buffalo are infected with BTB via aerosol transmission (Bengis, 1999). Vertical  
12 (intrauterine) and psuedovertical transmission (through infected milk) may occur but appear to  
13 be rare events (Bengis, 1999). The pathology of BTB in lions suggests that they acquire the  
14 disease by consuming infected buffalo (Keet et al., 1996), and it remains unclear how the effects  
15 of BTB, with its wide range of potential hosts, will ripple through the KNP ecosystem.

16 Due to the potential effects of BTB on buffalo and alternative host species, KNP  
17 managers would like to control or eradicate BTB via culling, vaccination, or some combination  
18 of the two. Previous modeling work on BTB in buffalo suggests that BTB may persist even when  
19 the buffalo population is reduced to low densities, making random culling, for the purpose of  
20 eradication, problematic (Rodwell, 2000). Thus, vaccination, or some combination of  
21 vaccination and culling, is a more attractive management option. Early action is likely to be the  
22 most effective, however there are many uncertainties surrounding the potential impacts (or lack  
23 thereof) of BTB on the buffalo population, the efficacy and duration of the vaccine in buffalo,

1 and the logistic difficulties of a vaccination program. Here we use an epidemiological model to  
2 tackle some of these questions surrounding management of the disease using the best available  
3 data. Analysis of the model provides the rapid answers required by managers and helps to focus  
4 further research projects.

5       Vaccination trials with Bacille Calmette-Guérin (BCG) and buffalo are currently  
6 underway in the KNP as the vaccine has been shown to give protection to cattle, deer, brushtail  
7 possums, ferrets, and badgers (for a review see Suazo et al., 2003). In cattle, BCG has been used  
8 in a number of trials and the amount of protection has varied widely (e.g. Francis, 1958;  
9 Berggren, 1977; Rodrigues et al., 1993; Colditz et al., 1994; Buddle et al., 1995c). More recent  
10 BCG vaccination trials in New Zealand have demonstrated up to 70% protection in cattle  
11 (Buddle *et al.* 1995c), data on the longevity of protection of the BCG vaccine, however, are non-  
12 existent in buffalo and limited in cattle (Berggren, 1977). Here we use an SEI (Susceptible-  
13 Exposed-Infectious) epidemic model to assess the potential effectiveness of a buffalo vaccination  
14 program.

15       Several models of BTB in wildlife and cattle have been published previously (for a  
16 review see Smith, 2001), but this is the first study to assess the efficacy of a vaccination program  
17 for African buffalo. The effectiveness of control programs in African buffalo is likely to differ  
18 from other wildlife and cattle for several reasons. First, African buffalo tend to live longer than  
19 other wildlife species that are infected with BTB (e.g. badgers, possums, and deer). Second,  
20 BTB appears to have only minor effects upon the survival of buffalo (Rodwell et al., 2001). As a  
21 result, BTB can reach high prevalence (60-92%) in buffalo herds (Bengis, 1999; Rodwell et al.,  
22 2000; Jolles, 2004). In contrast, a model of BTB transmission within cattle herds suggested that  
23 within-herd transmission alone was insufficient to maintain the infection (Barlow et al., 1997).

1 In badgers and possums the prevalence of BTB has tended to be less than 20% (Smith, 2001).  
2 Due to these differences with previously analyzed systems and the current effort to evaluate and  
3 implement a vaccination program to control BTB in African buffalo, we combine field data and  
4 mathematical modeling techniques to assess the likely success of a vaccination program.

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

21 We present preliminary analyses of field data to estimate dispersal and survival rates  
22 using data on over 130 radio-collared buffalo from November 2000 to December 2003. These  
23 estimates are then supplemented with published information on cattle and buffalo. The model is

1 then used to assess the potential efficacy of a vaccination program and highlight the importance  
2 of several model parameters. For the model, we assume that the vaccine protects individuals in  
3 any sex and age category completely, but that protection may wane over time. Even though an  
4 effective vaccine with these characteristics is not yet available, our model can be used to assess  
5 what elements are necessary for a successful vaccination program.

6       The technical part of this paper begins with a presentation of a discrete time SEI model.  
7 This model builds upon previous models of bovine tuberculosis in cattle and wildlife (e.g. Bentil  
8 and Murray, 1993; Ruxton, 1996; Barlow et al., 1997; Kao and Roberts, 1999; Smith et al.,  
9 2001) by incorporating dispersal, vaccination, sex, and age structure. Next, we outline the  
10 parameter estimation procedures and conduct sensitivity analyses of the model to determine  
11 which parameters explain the most variability in disease prevalence and eradication. We then  
12 further investigate the model in a single herd context (*i.e.* without dispersal to a background  
13 population). Finally, we assess the potential effectiveness of a vaccination program and whether  
14 it can be improved by focusing on different sex and age categories.

15

## 16 **2. Methods**

### 17 *2.1. Simulation model*

18 The model presented here is an age- and sex-class elaboration of a discrete time SEI epidemic  
19 model for a focal buffalo herd in contact with a background population. We use a one-month  
20 time step to account for the annual reproduction and vaccination of buffalo and the within-year  
21 transmission dynamics of BTB. Let  $X$ ,  $Y$ ,  $Z$  and  $V$  represent the number of individuals  
22 respectively susceptible to infection, exposed but not yet infectious, infectious, and vaccinated,  
23 and let  $N=X+Y+Z+V$  represent the total number of individuals. We assume that exposed

1 individuals ( $Y$ ) become infectious at a constant “incubation rate”  $\gamma$ . A proportion  $\psi(t)$  of the  
2 population is vaccinated every June, and a constant proportion  $\delta$  of the vaccinations fail in each  
3 month.

4       Currently available vaccines require the use of a helicopter to dart or drive the buffalo  
5 into pens prior to vaccination. With either method, an individual’s disease status is unknown  
6 prior to capture. We account for this logistic difficulty by allowing for repeat vaccinations as  
7 well as the vaccination of already infectious individuals. Thus one measure of the efficiency of a  
8 vaccination program is the percentage of individuals captured that are successfully vaccinated for  
9 the first time (*i.e.* the percentage of individuals not infected nor previously vaccinated). We  
10 compare management strategies based on the ratio of successful to total vaccinations, assuming  
11 that vaccination protects only susceptible individuals.

12       We assume that a fixed proportion  $\varepsilon$  of individuals emigrate from the focal herd to a pool  
13 of individuals outside the herd each month. We do not consider the herd structure or  
14 demographics of this background population, but assume that during each month the same  
15 number of individuals,  $I$ , immigrate to as emigrate from our focal herd. Further, we assume a  
16 constant proportion of the immigrants are susceptible ( $p_x$ ), exposed ( $p_y$ ), infectious ( $p_z$ ), and  
17 vaccinated ( $p_v$ ) for the duration of each simulation. This would be equivalent to vaccinating a  
18 focal herd that is embedded in a background population that is either in equilibrium or being  
19 maintained at some reduced prevalence. The model can then be used to inform managers about  
20 the effects of reducing movement between the focal herd and background population as well as  
21 reducing the prevalence of infection in the background population.

22       To incorporate sex and age structure, let  $j = 1, 2$  represent the sex (1=male, 2=female)  
23 and  $i = 1, \dots, 18$  the age class. We assume that a smaller proportion ( $s^{\bar{z}}$ ) of infectious individuals

1 (Z) survive each time period than healthy individuals and that the survival of calves depends  
 2 upon the total population size. We control the relationship between annual and monthly time  
 3 using the index  $r$  defined by the statement

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

5 Assuming events occur in the following order: vaccination ( $\psi$ ), transmission ( $\beta$ ), vaccine failure  
 6 ( $\delta$ ) and disease incubation ( $\gamma$ ), emigration and immigration ( $\varepsilon$ ), and survival ( $s_{ij}$ ), the monthly  
 7 model equations conforming to the above assumptions are:

$$8 \quad X_{i+r,j}(t+1) = s_{i,j}(N(t)) \left( 1 - \varepsilon_{i,j} \right) \left( 1 - \frac{\beta \sum_{i=1}^{18} \sum_{j=1}^2 Z_{i,j}(t)}{N(t)^\theta} \right) \left( 1 - \psi_{i,j}(t) \right) X_{i,j}(t) + \delta V_{i,j}(t) + p_x I_{i,j}(t)$$

$$9 \quad Y_{i+r,j}(t+1) = s_{i,j}(N(t)) \left( 1 - \varepsilon_{i,j} \right) \left( \frac{\beta \sum_{i=1}^{18} \sum_{j=1}^2 Z_{i,j}(t)}{N(t)^\theta} \right) \left( 1 - \psi_{i,j}(t) \right) X_{i,j}(t) + (1 - \gamma) Y_{i,j}(t) + p_y I_{i,j}(t)$$

$$10 \quad Z_{i+r,j}(t+1) = s_{i,j}^z(N(t)) \left( (1 - \varepsilon_{i,j}) (\gamma Y_{i,j}(t) + Z_{i,j}(t)) + p_z I_{i,j}(t) \right)$$

$$11 \quad V_{i+r,j}(t+1) = s_{i,j}(N(t)) \left( (1 - \varepsilon_{i,j}) (1 - \delta) (V_{i,j}(t) + \psi_{i,j}(t) X_{i,j}(t)) + p_v I_{i,j}(t) \right)$$

$$12 \quad I_{i,j}(t) = \varepsilon_{i,j} (X_{i,j}(t) + Y_{i,j}(t) + Z_{i,j}(t) + V_{i,j}(t))$$

13 Annual reproduction is handled through the following statement that implicitly assumes an equal  
 14 sex ratio at birth: IF mod( $t,12$ )=0 THEN for  $j= 1$  or  $2$ ,

$$15 \quad X_{1,j}(t) = \sum_{i=1}^{18} \frac{b_i}{2} (X_{i,2}(t) + Y_{i,2}(t) + Z_{i,2}(t) + V_{i,2}(t)), \quad Y_{1,j}(t) = 0, \quad Z_{1,j}(t) = 0, \quad \text{and} \quad V_{1,j}(t) = 0, \quad \text{where } b_i \text{ is}$$

16 the expected number of offspring per female each calving cycle (approximated to be in January  
 17 each year). Following Rodwell et al. (2001) in the KNP, we assume that BTB does not affect  
 18 fecundity, although Jolles (2004) showed some effect of BTB on the fecundity of young and old

1 buffalo, but not prime-aged buffalo from five to eight years old. Disease transmission in the  
 2 model depends on  $1/N^\theta$  (Anderson and May, 1992), which is frequency-dependent when  $\theta$   
 3  $=1$  and density dependent when  $\theta=0$ . Population size in this model is relatively constant, so that  
 4 selecting  $\theta=0$  or  $1$  is essentially equivalent to rescaling the transmission coefficient  $\beta$ . Thus, the  
 5 value of  $\theta$  is not critical to our analysis and we present results only for the case  $\theta=1$ .

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

$$11 \quad s_{i,j}(N(t)) = \frac{s_0}{1 + \left(\frac{N(t)}{\kappa}\right)^\phi}, \quad i=1, \quad j=1,2$$

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

$$18 \quad s_{i,j}^z(N(t)) = \frac{s_0 - \alpha_0}{1 + \left(\frac{N(t)}{\kappa}\right)^\phi}, \quad i=1, \quad j=1,2$$

1 Finally, we assumed that adult survival is constant over time, but depended upon the age, sex,  
2 and disease status of the animal, whereby the survival of infectious individuals was reduced by  
3  $\alpha_1$ . We assumed that all buffalo in the 18<sup>th</sup> age-class died at the end of each year.

4

## 5 *2.2. Parameter estimation*

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

22

1 2.2.1. *Survival*

2 We assumed that calf survival ( $s_{1j}$ ) was density dependent and the maximum possible calf  
3 survival ( $s_0$ ) was one (see above). Survival estimates for the other sex and age categories were  
4 estimated from field data with known-fate models in program MARK using BTB-status, age, and  
5 gender as individual covariates (White and Burnham, 1999). The dataset consisted of 132 radio-  
6 collared buffalo from May 2001 to November 2003. Twenty-two buffalo were BTB-positive on  
7 the first test. Thirteen animals that converted from BTB-negative to positive were reclassified as  
8 positive individuals at the time of their first positive test. We assumed buffalo were BTB-  
9 negative if they were a multiple, equal, or avian reactor on the gamma-interferon test. For model  
10 selection of the survival data, we used AICc, which is a modified version of Akaike's  
11 Information Criterion (AIC) that corrects for small sample sizes relative to the number of  
12 parameters (Burnham and Anderson, 2002). The AIC approach is a method of comparing the  
13 goodness-of-fit of nested and non-nested models and discourages the use of models with too  
14 many parameters that overfit the data. The minimum and maximum values shown in Table 1 are  
15 the 95% confidence intervals for each parameter using the delta method (White and Burnham,  
16 1999).

17

18 2.2.2. *Dispersal* ( $\epsilon$ )

19 Previous studies suggest that only adult males move between herds (Sinclair, 1977; Prins, 1996).  
20 Using radio-tracking data of 120 buffalo in four herds from May 2001 to December 2003, we  
21 estimated the movement rate of buffalo between a focal herd and background population. We  
22 found lower cohesion amongst buffalo herds of the KNP than past studies (Cross et al., 2005). At

1 the start of the study, the study area appeared to contain four herds that separated and re-fused  
2 over time. Three of those herds fragmented and fused with herds in other areas of the KNP, thus  
3 making it difficult to define a dispersal event because the herd “dispersed” as a unit. As a  
4 minimum estimate of dispersal, we used the individuals in the remaining cohesive herd to  
5 estimate the probability of an individual moving from a focal herd to other herds in the  
6 background population. Individuals were assigned a value of zero or one respectively for every  
7 month they were present in the focal herd and either dispersed to another herd or remained in the  
8 focal herd. These data were then used in logistic regression analyses with sex and age as  
9 covariates. We excluded those dispersal events that lasted for less than one week because short  
10 duration events are unlikely to result in many disease transmission events. Animals were grouped  
11 into the following age categories: 1-2, 3-4, 5-7, and 8+ yrs old.

### 12 *2.2.3. Disease transmission ( $\beta$ )*

13 The transmission coefficient was estimated by fitting the model to the observed 1998 BTB  
14 prevalence values for the KNP (Rodwell et al., 2000). The model was parameterized with the  
15 baseline values in Table 1 and started with a disease prevalence of either 0.04 or 0.29 to  
16 correspond to the prevalence of BTB in the central and southern regions of the KNP in 1991. The  
17 initial population size was 250, to match the average herd size of the KNP (Whyte, unpublished  
18 data), and distributed among age classes to correspond to the stable age distribution predicted by  
19 the demographic component of the model. The model was run for 7 years and  $\beta$  was adjusted to  
20 minimize the sum of squared residuals between the predicted and observed prevalence in 1998.  
21 Transmission coefficient values that resulted in predicted 1998 prevalence values within the  
22 empirical 95% confidence intervals for the south and central regions were used to establish the  
23 minimum and maximum values in Table 1. Simulations assumed a closed population and no

1 vaccination. Data from the northern region of the KNP were not used to parameterize  $\beta$  because  
2 no BTB-positive individuals were sampled in that area prior to 1998.

3

#### 4 2.2.4. Other model parameters

5 The pathology of BTB in buffalo and cattle suggests that BTB lesions are not encapsulated by  
6 the immune system and individuals are probably infectious within a few months of infection (De  
7 Vos et al., 2001). Neill *et al.* (1991) estimated the latency period of BTB in cattle to be 87 days,  
8 which translates to a monthly incubation rate  $\gamma$  of 0.21 (Table 1). Due to the limited data  
9 available on incubation rate,  $\gamma$ , we chose a wide range of 0.056 to one for the sensitivity analyses.  
10 Since  $\phi$  is probably between two and six (see discussion in Getz, 1996), we used a value of four  
11 and adjusted  $\kappa$  to yield a stable herd size of around 250 individuals. Given the limited data  
12 available on the duration of vaccine protection in buffalo and the indication in Berggren (1977)  
13 and Francis (1947) that protection wanes in vaccinated cattle between one and five years, we  
14 explored a wide range of vaccine failure rates from lifelong protection (*i.e.*  $\delta=0$ ) to a half-life of  
15 one year.

16

#### 17 2.3. Sensitivity analyses

18 Sensitivity analyses were conducted using Monte Carlo methods to assess the relative  
19 effects of several model parameters. Specifically, 10,000 random parameter sets were created by  
20 choosing  $\psi$ ,  $\delta$ ,  $\beta$ ,  $\gamma$ ,  $\epsilon_{i,j}$ ,  $p_z$ ,  $s_{i,j}$ ,  $\alpha_0$  and  $\alpha_1$  from uniform distributions bounded by the minimum  
21 and maximum values shown in Table 1. We assumed that the vaccine was 100% protective for  
22 this analysis. . Each parameter set was used to run the deterministic model once. The prevalence

1 at year 50 was recorded for each run and used as the dependent variable in multiple linear  
2 regressions where model parameters were the explanatory variables (Wisdom and Mills, 1997;  
3 Wisdom et al., 2000; Cross and Beissinger, 2001). To facilitate comparisons between parameters  
4 measured on different scales all model parameters were transformed to percentage difference  
5 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  
6 mean) prior to statistical analysis. Subsampling this dataset and evaluation of standard errors  
7 revealed that 10,000 runs were sufficient to solidify the ranking hierarchy of the top six model  
8 parameters in the statistical analyses. The other eight parameters in the sensitivity analysis  
9 explained little variability in either disease prevalence or quasi-eradication, had large standard  
10 errors, and were omitted from Table 2.

11 Model parameters were ranked according to the magnitude of their standardized  
12 coefficients (*i.e.* the regression coefficient divided by its standard error), which is a unitless  
13 quantity expressing the unique contribution of that variable scaled by the estimation uncertainty  
14 (Selvin, 1995). Model parameters that are good predictors of disease prevalence may be different  
15 from those that are good predictors of disease eradication. Logistic regression was used to  
16 identify the latter parameters (McCarthy et al., 1995; Cross and Beissinger, 2001). For the  
17 logistic regression analysis, disease prevalence at year 50 was converted to a binary variable of  
18 disease persistence or eradication. We used a prevalence of 5% as the quasi-eradication threshold  
19 because very few parameter sets resulted in quasi-eradication at lower threshold values making  
20 maximum likelihood estimation difficult in the logistic regression analysis. As in the linear  
21 regression analysis, each model parameter was transformed to percentage difference from the  
22 mean and individually used to predict disease eradication at year 50. All simulations started with  
23 250 individuals in a stable-age distribution and an initial prevalence of 0.05, evenly distributed

1 amongst all sex- and age-classes. The epidemiological model was coded in Matlab 5.3  
2 (Mathsoft™) and statistical analyses were conducted using S-Plus 6 (Insightful Corp, 2001).

3

### 4 **3. Results**

#### 5 *3.1 Field data parameter estimates*

6 Our survival data indicated that males and individuals over 8 yrs old had lower survival  
7 rates than females and those under 8 yrs old (Table 1). Age category (1-7 vs. 8+) and gender  
8 were statistically significant explanatory variables in likelihood ratio tests (LRT) where we  
9 included one variable at a time ( $p=0.004$  and  $0.001$ , respectively;  $df=1$ ) and were supported in  
10 AICc analyses. There was little statistical support for the inclusion of more refined age  
11 categories using either AIC or LRT methods. Our analyses did not indicate any additional  
12 mortality amongst the 35 BTB-positive animals ( $df=1$ ,  $p=0.19$ ). Even though this is based on  
13 only the first two years of data, this result, in combination with previous cross-sectional analyses,  
14 suggests that the annual disease induced mortality associated with BTB is probably between zero  
15 and 10 percent (Rodwell et al., 2000; Jolles, 2004). Statistical model comparisons using AICc  
16 values and sex, age (1-7yrs, 8+), and BTB-status as explanatory variables indicated that the  
17 additive sex+age model provided the best fit to the survival data. A sex\*age model was the only  
18 other model that appeared to be supported by the data ( $\Delta AICc = 0.869$ ). Using the sex+age  
19 model we estimated the survival rates shown in Table 1.

20 In contrast to previous studies of buffalo, we found that all sex and age groups moved  
21 between herds, albeit adult males moved between herds more frequently than young males and  
22 females (Table 1, Fig. 1). Logistic regression analyses indicated a significant age\*sex interaction  
23 ( $p=0.02$ ,  $df=3$ , deviance = 9.88) whereby males over 8 yrs old were more likely to disperse

1 (Table 1, Fig. 1). Due to the similar dispersal rates of females and juvenile males we aggregated  
2 these sex and age categories and reran the logistic model before calculating the dispersal rates in  
3 Table 1.

4

### 5 *3.2 Sensitivity analyses*

6         Sensitivity analyses of this model around the baseline set of parameter values indicate  
7 that for the model and parameter space presented, disease prevalence in the background  
8 population,  $p_z$ , is the primary factor determining the BTB prevalence in the focal herd (Table 2,  
9  $r^2 = 0.95$ ). Vaccination rate  $\nu$  and the transmission coefficient  $\beta$  were the second and third  
10 parameters in the ranking hierarchy, while survival rates explained very little variability in BTB  
11 prevalence or eradication. There were few differences in the ranking of the top five parameters  
12 between the linear and logistic regression results indicating that parameters that regulate  
13 prevalence also determine the probability of eradication.

14

### 15 *3.3 Model results without dispersal*

16         To assess the effects of other variables we analyzed the model in the context of a single  
17 herd without dispersal (such as a cattle herd or small reserve). Using the baseline values in Table  
18 1, the model predicts that BTB should reach an asymptotic prevalence of  $\sim 0.44$  in a herd of  $\sim 250$   
19 individuals, and as would be expected of a chronic disease without recovery, the model does not  
20 exhibit any cyclical behavior (Fig. 2). Optimal vaccine strategies depend on the distribution of  
21 vaccinations to different sex and age categories and the duration of vaccine protection. Assuming  
22 that the vaccine grants lifelong protection, the model suggests that control programs should focus

1 upon younger individuals. In particular, focusing the control strategy on younger individuals  
2 produces a higher ratio of successful to total vaccinations (*i.e.* less wasted vaccinations) than  
3 vaccinating individuals in proportion to the age structure of the population (Fig. 3). As vaccine  
4 duration decreases, however, the advantages of vaccinating juveniles decreases and the lines on  
5 Fig. 3 approach the efficiency of the calf-only vaccination strategy. In other words, when the  
6 vaccine lasts for shorter amounts of time there are fewer redundant vaccinations of older  
7 individuals. Few differences exist between the efficacy of male or female vaccination programs  
8 of a focal herd without dispersal (Fig. 3). However, in model simulations with dispersal (data not  
9 shown) vaccination programs were more effective if they focused on females because  
10 vaccinations of dispersing males were, in effect, wasted with respect to reducing prevalence in  
11 the focal herd.

12         In the best-case scenario of a 100% effective vaccine that provides life-long protection, a  
13 vaccination program focusing upon calves would require the vaccination of around 70% of the  
14 calves every year to eradicate (*i.e.* prevalence < 1%) BTB by year 50 (Fig. 4a). A program  
15 focused on the entire population would require a vaccination rate of less than 30% for  
16 eradication (Fig. 4a). However, 70% of the calf population translates into ~1300 vaccinations  
17 over a 50-year period; whereas, 30% of the total population translates into ~3100 vaccinations  
18 over the same time period in a herd of approximately 250 individuals. Thus a calf-only policy  
19 requires higher coverage of that age-class but fewer vaccinations in total. This is not surprising  
20 given that calves are approximately 16% of the total population and we have assumed lifelong  
21 vaccine protection.

22         Given that vaccination rate  $\psi$  and vaccine failure rate (also expressible in terms of the  
23 half-life of the vaccine)  $\delta$  are two parameters that may be altered by managers or scientists, we

1 calculated BTB prevalence at year 50 for different combinations of these parameters and calf-  
2 only vaccination program (Fig. 5). Model results suggest that if 70% of the calf population is  
3 vaccinated every year BTB would may be eradicated by year 50 assuming the vaccine granted  
4 lifelong protection and no migration between the focal herd and background population. If the  
5 half-life of the vaccine was less than five years, however, a vaccination program is unlikely to  
6 eradicate the disease by year 50 (Fig. 5).

7

#### 8 **4. Discussion**

9       The management issues surrounding bovine tuberculosis in the Kruger National Park of  
10 South Africa are typical of many invasive species and emerging infectious diseases. Immediate  
11 actions are more likely to be effective, but limited data are available upon which to base  
12 management and research decisions. We used field data to bound the range of possible parameter  
13 values and simulated an SEI disease model to assess the importance of different model  
14 parameters and the effectiveness of vaccination as a control strategy. Our results, based upon the  
15 first analysis of a dynamic epidemiological model of BTB in a buffalo population, indicate that  
16 vaccination alone is unlikely to be an effective management tool to eradicate BTB. The  
17 literature on modeling BTB in other species is extensive and conclusions vary, but, in general,  
18 our conclusions about the utility of vaccination is in contrast with more encouraging modeling  
19 studies on vaccination of BTB in possums, badgers, and cattle (Barlow, 1991; White and Harris,  
20 1995; Roberts, 1996; Kao et al., 1997; Tuytens and MacDonald, 1998; Smith, 2001; Smith and  
21 Cheeseman, 2002; Wilkinson et al., 2004). This difference may be due to the high prevalence of  
22 BTB in African buffalo (>50%; Rodwell et al., 2000) compared to <20% for badgers and  
23 possums (Krebs et al., 1997; Woodroffe et al., 1999; Coleman and Cooke, 2001).

1           Our model predicts that BTB should reach an asymptotic prevalence of around 44%  
2 assuming a closed population and a relatively constant herd size of 250 individuals (Fig. 2). Data  
3 from one herd in the southeastern corner of the KNP suggests that this estimate of asymptotic  
4 prevalence may be low. The Mpanamana herd of the KNP had a stable prevalence of 67% in  
5 1992 and 1996 (De Vos et al., 2001). In addition, Jolles (2004) estimated the asymptotic BTB  
6 prevalence to be 53% (95% CI = [49-58%]) in Hluhluwe-Umfolozi Park. Additional data on  
7 BTB prevalence and transmission rates would help discern whether our parameter estimates or  
8 model structure should be modified to match the higher prevalence seen in these two herds. If  
9 this is the case, then our model results may represent conservative estimates of the vaccination  
10 effort necessary to control and eradicate BTB.

11           Assuming frequency-dependent transmission and a vaccine that is equally effective and  
12 protective across all sex- and age-classes, vaccination programs will be most effective in  
13 reducing prevalence in the focal population if they focus on calves (Figs. 3 and 4). Younger  
14 individuals are unlikely to be infected or previously vaccinated, thus increasing the ratio of  
15 successful to total vaccinations (Fig. 3). Also, younger individuals will, on average, remain  
16 longer in the population than older individuals. Therefore, vaccinated calves will contribute more  
17 to herd immunity than vaccinated adults. The BCG vaccine has been the most comprehensively  
18 tested BTB vaccine in wildlife and cattle (e.g. Ellwood and Waddington, 1972; Waddington and  
19 Ellwood, 1972; Berggren, 1977; Aldwell et al., 1995; Buddle et al., 1995a; Buddle et al., 1995b;  
20 Buddle et al., 1995c; Buddle et al., 1997). Due to the fact that the efficacy of the BCG vaccine  
21 may be reduced by prior exposure to environmental mycobacteria (Buddle et al., 1995a; Fine,  
22 1998), BCG vaccination may also be most effective in the younger age groups. Thus the

1 vaccination of younger rather than older individuals is supported for both biological and  
2 mathematical reasons (Fig. 3).

3       Even in the best-case scenario of a 100% effective vaccine with lifelong protection, a  
4 management program focused on calves would need to vaccinate around 70% of calves every  
5 year to eradicate BTB by year 50 (Fig. 4a). In a herd of 250 buffalo this translates to around  
6 1500 vaccinations over a 50-year period (Fig. 4b). Our predictions may be overly optimistic  
7 since we assumed that all vaccinated individuals were protected against infection and our  
8 estimated asymptotic herd prevalence may be lower than that observed in the field. Given that:  
9 (1) the current BCG vaccine is very unlikely to be 100% effective in buffalo, (2) that protection  
10 probably wanes over time (Berggren, 1977; Buddle et al., 2000), (3) that drug and labor costs for  
11 vaccinating a buffalo are over \$100 (US) per individual, and (4) a high percentage of individuals  
12 must be vaccinated to eradicate the disease, the eradication of BTB via vaccination alone is  
13 probably not an effective management strategy. Vaccination may be useful to control BTB at  
14 lower prevalence levels, but then the question arises as to whether the cost of an indefinite  
15 control program outweighs the benefit in reduced prevalence. At this point, we cannot answer  
16 this question because it rests upon the effect of BTB on lion populations and the relationship  
17 between the prevalence of BTB in lions and buffaloes. Additional work on the interaction of  
18 lions, buffaloes, and BTB, and the degree to which lions select for BTB-positive individuals  
19 would be enlightening. Further, additional modeling work is necessary to assess the potential  
20 effectiveness of vaccination, in combination with other control measures such as a test-and-  
21 remove program, in a spatial context.

22       Sensitivity analyses suggest that disease incubation ( $\gamma$ ) and buffalo survival rates were  
23 relatively unimportant model parameters (*i.e.* they explained very little variability in the

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

12         We parameterized the epidemiological model using previously published parameter  
13 estimates as well as data from a longitudinal study of radio-collared individuals in the central  
14 region of the KNP. The dispersal and survival rate estimates presented here are the first estimates  
15 based upon longitudinal studies of known radio-collared individuals. Previous estimates were  
16 based upon cross-sectional life-table analyses and/or a few known, but unmarked individuals  
17 (Sinclair, 1977; Prins, 1996; Jolles, 2004). Analysis of the longitudinal dataset of known  
18 individuals indicated that dispersal rate varied by sex and age, whereby males over eight years  
19 old were the most likely to disperse from the focal herd (Table 1, Fig. 1). In contrast to previous  
20 studies, we found females and juvenile males also moved between mixed herds via splinter  
21 groups when herds split and later fused with other herds (Cross et al., 2004; Cross et al., 2005).  
22 We began the study with four herds in the study area. Since 2001 these four herds have  
23 splintered into as many as 13 herds and only one of the original herds remained as a cohesive

1 unit within the study region. As a result it is difficult to define dispersal events when the herd  
2 itself is changing. We used the one cohesive herd to estimate dispersal rates, which, given the  
3 fluid and mobile nature of the other herds, should be seen as minimum estimates and highlights  
4 the importance of developing spatial models of disease spread.

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

20 The model presented here is based upon best empirical data currently available and  
21 provides an objective view of the likely effectiveness of a vaccination strategy as well as  
22 highlights important research and management issues. The importance of the background  
23 population in the sensitivity analysis suggests that managers should view herds, or parks, as open

1 systems and incorporate the surrounding populations into their control strategies, and the degree  
2 to which such invasions must be controlled depends on the background prevalence of the  
3 disease. Further, researchers should focus on spatial disease models to incorporate individuals'  
4 movement patterns. The inclusion of spatial complexity into our model, and more data on  
5 transmission rates and the inter-herd movement patterns of individuals are needed to assess the  
6 likely efficacy of a combined vaccination and selective removal of infected individuals in  
7 containing the spread of BTB in African buffalo. Nonetheless, the model presented here suggests  
8 that even in the best case scenario, vaccination alone is unlikely to be an effective control  
9 strategy for BTB in buffalo, and thus research and managers should focus on other possible  
10 methods to control the spread of this exotic disease.

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- 15

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

5  
6 Fig. 2. Predicted BTB prevalence plotted as a function of time using the upper, lower and  
7 baseline values of the transmission coefficient ( $\beta = 0.034, 0.043, 0.053$ ). Simulations assume a  
8 closed population and no vaccination effort.

9  
10 Fig. 3. The number of successful vaccinations for the indicated vaccination strategies (*i.e.*  
11 focusing on calves, juveniles, males, females or the entire population) plotted as a function of the  
12 total vaccinations in a herd by year 50. “Successful” is defined as the vaccination of uninfected  
13 and previously unvaccinated individuals. “All” indicates a management strategy that vaccinates  
14 all individuals in proportion to their abundance in the population. Simulations assume a closed  
15 population and lifelong vaccine protection.

16  
17 Fig. 4. Prevalence of BTB at year 50 plotted as a function of (a) vaccination rate and (b)  
18 cumulative vaccinations to demonstrate the importance of focusing vaccination effort on calves.  
19 Simulations assume a closed population, vaccination in proportion to abundance in the focal  
20 population, and lifelong vaccine protection.

21  
22 Fig. 5. Prevalence isopleths at year 50 as a function of vaccination rate and vaccine half-life.  
23 Simulations assume a closed population and an annual calf-only vaccination program. Vaccine

- 1 half-life refers to the amount of time before half of the vaccinated individuals are susceptible
- 2 again.

Table 1. Parameter estimates used in the buffalo vaccination model.

Parameter	Symbol	Minimum	Baseline	Maximum	Source
<i>Annual buffalo survival</i>					
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	$\kappa$	--	400	--	see text
Abruptness parameter	$\phi$	2	4	6	2
<i>Annual buffalo reproduction</i>					
Cows 3-4	$r_3$	--	0.51	--	3
Cows 4-5	$r_4$	--	0.64	--	3
Cows 5+	$r_{5+}$	--	0.68	--	3
<i>Monthly dispersal</i>					
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
<i>Monthly disease parameters</i>					
Transmission coefficient	$\beta$	0.034	0.043	0.053	1
Incubation rate	$\gamma$	0.056	0.21	1	4
Reduction in maximum juvenile survival	$\alpha_0$	0	0.0043	0.0084	5
Reduction in adult survival	$\alpha_1$	0	0.0043	0.0084	5
Transmission exponent	$\theta$	0	--	1	see text
Vaccination rate	$\psi$	0	--	1	see text
Vaccine failure rate	$\delta$	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, de Vos et al. 2001; 5) Rodwell et al. 2001, Caron et al 2003, Jolles 2003; 6) unknown, but see Berggren 1977.

Table 2: Logistic and linear regression sensitivity analysis of 10,000 runs of the vaccination model using parameter values chosen from uniform distributions. All parameters were transformed to % change from the mean and only the six most important variable are shown.

Model parameter	Variable	Linear regression <sup>a</sup>		Logistic regression <sup>a</sup>	
		Coefficient	$b/SE^b$	Coefficient	$b/SE^b$
Background prevalence	$p_z$	0.222	476.5	-97.8	-13.0
Vaccination	$\psi$	-0.036	-77.1	3.0	9.3
Transmission coefficient	$\beta$	0.138	64.8	-16.8	-9.6
Reduction in adult survival	$\alpha_1$	-0.019	-39.4	2.1	7.0
Female and juvenile dispersal	$\varepsilon_{1-5,1;1+,2}$	0.026	32.7	3.0	6.2
Vaccine failure	$\delta$	0.013	27.1	-1.0	-4.1

<sup>a</sup> Multiple linear and logistic regressions with year 50 disease prevalence or eradication as the

<sup>b</sup> standardized coefficients were divided by the standard error to standardize measurements and

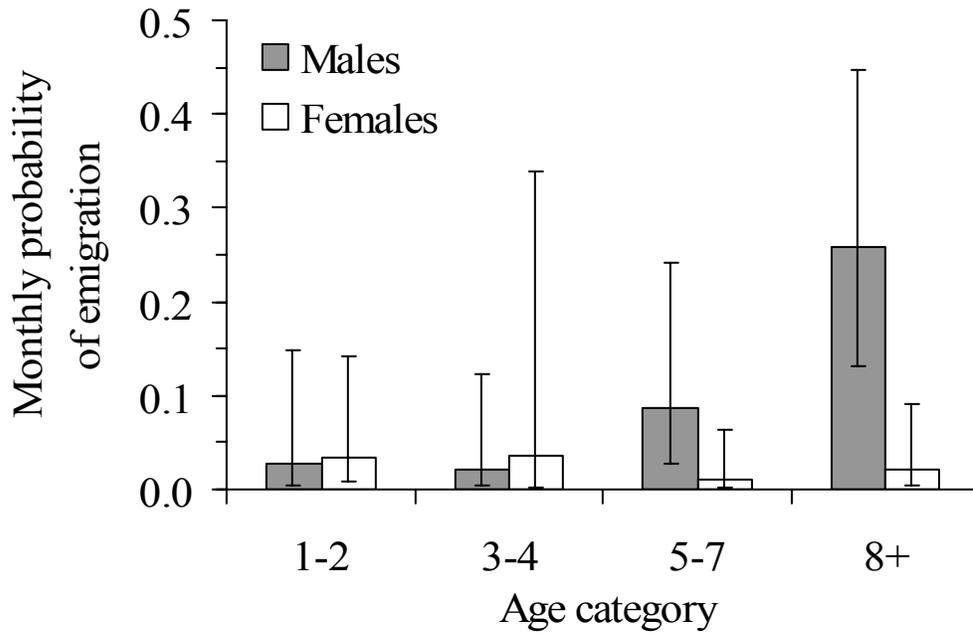


Fig. 1.

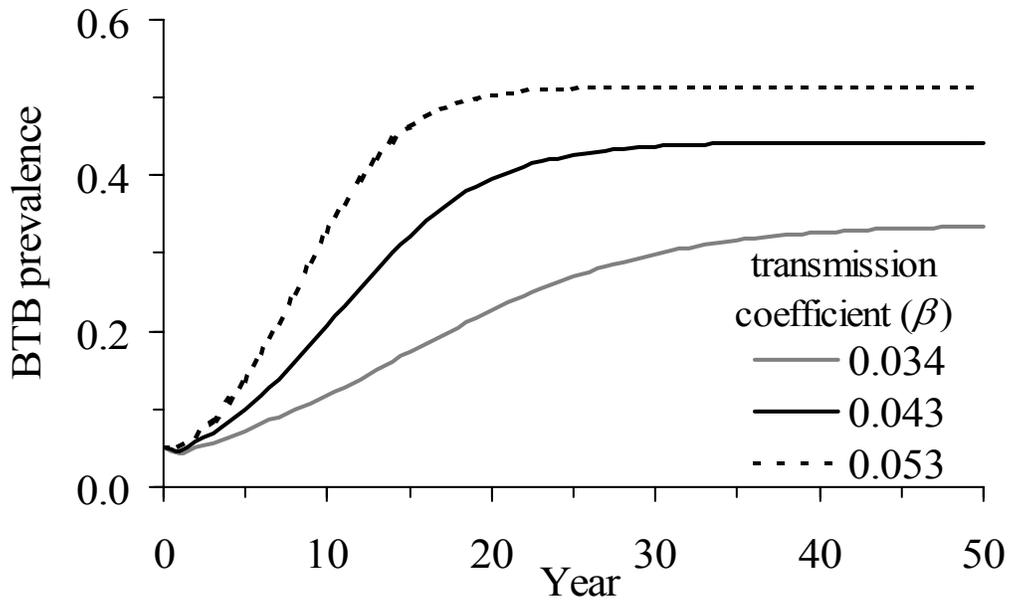


Fig. 2.

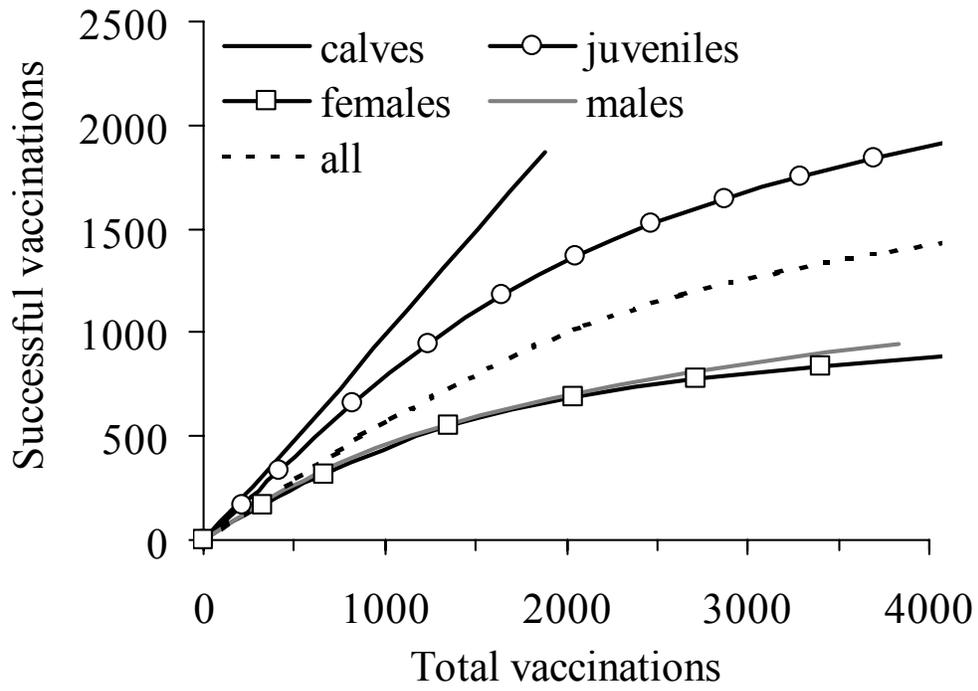


Fig. 3

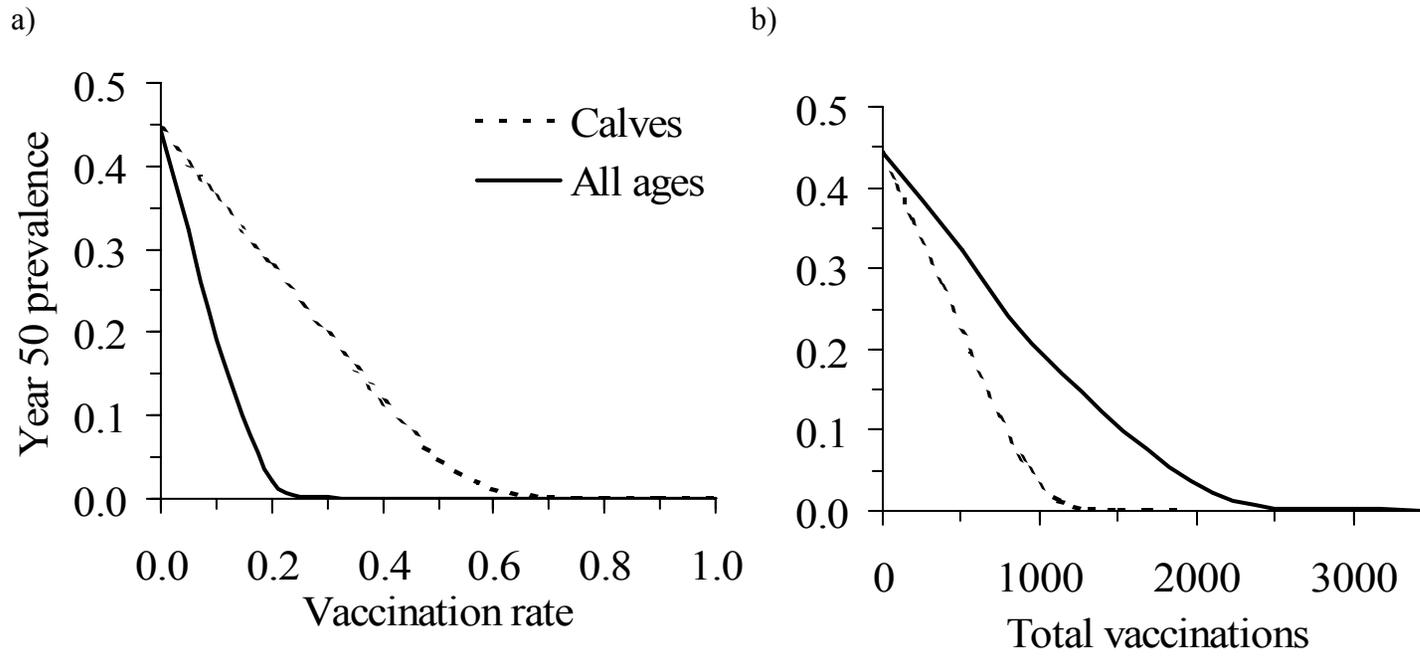


Fig. 4 a and b

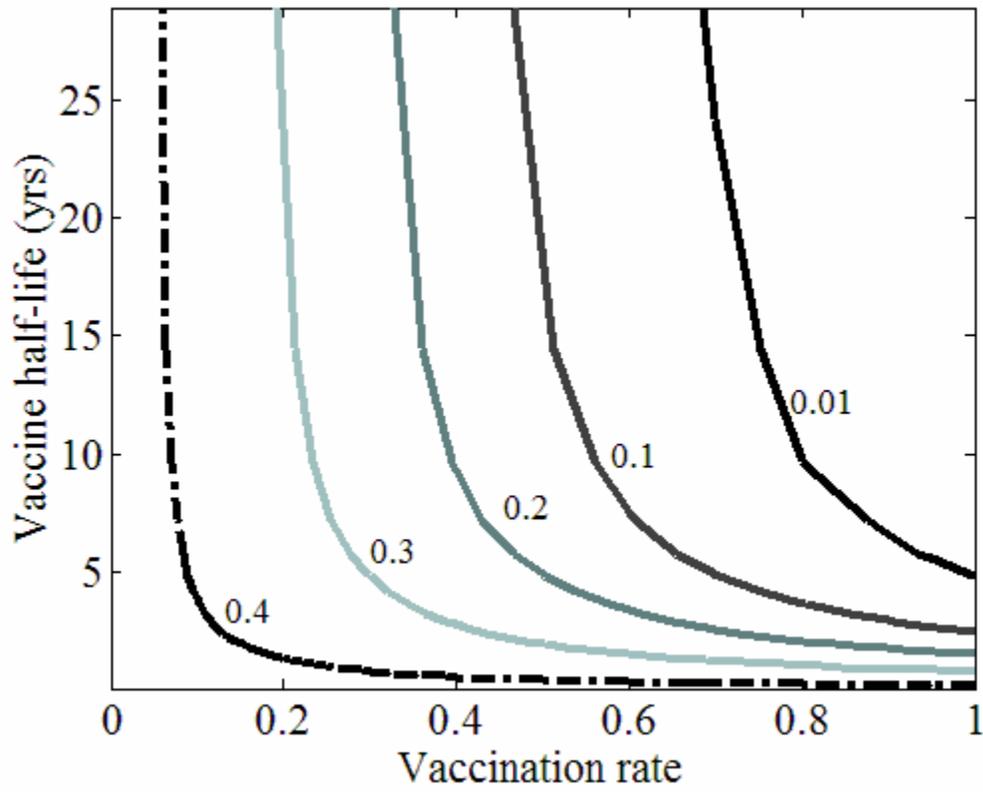


Fig. 5.