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REPORTS

HIDDEN EFFECTS OF CHRONIC TUBERCULOSIS IN AFRICAN BUFFALO

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Abstract. Infectious diseases can bring about population declines and local host extinctions, contributing significantly to the global biodiversity crisis. Nonetheless, studies measuring population-level effects of pathogens in wild host populations are rare, and taxonomically biased toward avian hosts and macroparasitic infections. We investigated the effects of bovine tuberculosis (bTB), caused by the bacterial pathogen *Mycobacterium bovis*, on African buffalo (*Syncerus caffer*) at Hluhluwe-iMfolozi Park, South Africa. We tested 1180 buffalo for bTB infection between May 2000 and November 2001. Most infections were mild, confirming the chronic nature of the disease in buffalo. However, our data indicate that bTB affects both adult survival and fecundity. Using an age-structured population model, we demonstrate that the pathogen can reduce population growth rate drastically; yet its effects appear difficult to detect at the population level: bTB causes no conspicuous mass mortalities or fast population declines, nor does it alter host-population age structure significantly. Our models suggest that this syndrome—low detectability coupled with severe impacts on population growth rate and, therefore, resilience—may be characteristic of chronic diseases in large mammals.

Key words: African buffalo; chronic disease; fecundity; mortality; Mycobacterium bovis; *population age structure; population growth rate; population resilience;* Syncerus caffer; *tuberculosis.*

INTRODUCTION

Emerging infections, involving novel pathogens or bringing established pathogens in contact with naïve host populations, can have drastic effects on their hosts (Daszak et al. 2000, Harvell et al. 2002, Altizer et al. 2003). In addition, pathogens capable of infecting multiple species may cause extinctions, as more-resistant host species act as reservoirs of infection, preventing the demise of the pathogen along with its susceptible hosts (Gog et al. 2002). Despite growing concern over the impact of diseases on wildlife conservation, population-level effects of pathogens in wild host populations have rarely been measured (Gulland 1995, Harvell et al. 1999), and most studies have focused on avian hosts and macroparasitic infections (Tompkins et al. 2002; but see Albon et al. 2002). Further, most wildlife-disease studies focus on catastrophic declines, often of endangered host populations, due to epidemic disease (e.g., Van Riper et al. 1986, Thorne and Wil-

liams 1988, Berger et al. 1998), while the population-level effects of less conspicuous, chronic diseases remain largely obscure.

Mycobacterium bovis causes chronic infection in a wide range of mammalian hosts. The pathogen is exotic to sub-Saharan Africa, and bovine tuberculosis (bTB) is emerging as a wildlife disease in southern Africa (de Lisle et al. 2002). Studies of bTB in wildlife have concentrated on badgers (*Meles meles*) in the United Kingdom (e.g., Tuyttens et al. 2000, Garnett et al. 2002, Donnelly et al. 2003), and brushtail possums (*Trichosurus vulpecula*) in New Zealand (e.g., Fulford et al. 2002, Ramsey et al. 2002, Caley and Hone 2004), due to their function as reservoirs of infection for livestock. These studies have yielded detailed information on the effects of bTB on badger and possum behavior and ecology. Such information is much sparser for free-roaming ungulate populations (but see Rodwell et al. 2001).

Our research was conducted at Hluhluwe-iMfolozi Park (HiP), South Africa, where bTB was first diagnosed in 1986 in a buffalo. The park has a buffalo population of approximately 3000 individuals, which appear to be the primary maintenance host for bTB. Park management have maintained an active bTB control program since 1999, which involves annual buffalo

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PLATE 1. African buffalo captured in Hluhluwe-iMfolozi Park, South Africa. The animals are held for three days for TB-testing. To administer the TB skin-test, buffalo are immobilized in small groups of 4–8 animals, for approximately ten minutes. The drugs are delivered using a pole syringe. Once they have been injected, the buffalo move into a larger compartment to settle down. TB-negatives are released back into the park; TB-positives are culled. Photo credit: A. Jolles.

round-ups for bTB testing, and culling of bTB-positive buffalo. Data presented here come from buffalo capture 2000 and 2001. This study is one of the first to demonstrate population-level effects of a chronic microparasitic infection in a wild mammalian host.

METHODS

Buffalo capture and disease survey

Buffalo capture and TB testing were conducted by KwaZulu-Natal Wildlife, the organization managing HiP (Hluhluwe-iMfolozi Park, South Africa; see Plate 1). Buffalo herds were chased into a capture corral set up within the park, using a helicopter. All captured animals were marked with brands to allow identification of recaptured animals in subsequent years. Buffalo were tested for TB using a skin test similar to that used to diagnose TB in humans. A small amount of mycobacterial protein (tuberculin) is injected subcutaneously in the buffalo's neck, and the thickness of the skin fold around the injection site is measured. When the test is read 72 h later, animals that have been exposed to mycobacterial infection show an antibody response, visible as a swelling at the injection site. The test is estimated to identify 80.9% of infected animals and 90.2% of uninfected animals correctly (J. P. Raath, *unpublished data*), which is similar to tuberculin-test sensitivity and specificity observed in cattle (80–91% and 95–100%, respectively; Lilenbaum et al. 1999, Llamazares et al. 1999, Ameni et al. 2000). Cross-reactivity of bovine tuberculin with immune responses to other mycobacteria, such as *Mycobacterium avium*, can yield false-positive results. To identify these cases and thus improve test specificity, we injected buffalo with avian tuberculin on the other side of their necks and considered weak reactions to bovine tuberculin in combination with strong reactions to avian tuberculin to indicate bTB (bovine tuberculosis) negative status. All TB testing was conducted by park and state veterinarians. TB-positive buffalo were slaughtered; negatives were released back into the park.

TABLE 1. Buffalo vital rates and elasticities of population growth rate λ to each parameter.

Parameter	Healthy value	TB-infected value	Elasticity of λ	Explanation
Fecundity				
Subadult	0.15	0.11	0.0043	annual likelihood that a female buffalo aged 4.5–5.5 yr bears a female calf
Young adult	0.37	0.37	0.0243	annual likelihood that a female buffalo aged 5.5–8.5 yr bears a female calf
Mature adult	0.37	0.27	0.0487	annual likelihood that a female buffalo aged 8.5–15.5 yr bears a female calf
Senescent	0.30	0.22	0.0138	annual likelihood that a female buffalo aged ≥16 yr bears a female calf
Survival				
Calf	0.73	0.73	†	likelihood that a newborn calf survives to age 6 mo
Juvenile	0.85	0.85	0.3640	likelihood of a juvenile buffalo aged 0.5–4.5 yr surviving to the next year
Adult	0.97	0.86	0.5109	likelihood of a buffalo aged 4.5–15.5 yr surviving to the next year
Senescent	0.74	0.63	0.0339	likelihood of a geriatric buffalo aged ≥16 yr surviving to the next year

† Calf survival to 0.5 years is factored into fecundity parameters in the model. Therefore, elasticity to calf survival is included in the elasticity values for fecundity and does not carry its own elasticity.

In animals up to five years old, age can be determined from tooth-emergence patterns, body size, and horn development. These criteria allow sorting immature buffalo into year cohorts (Grimsdell 1973, Sinclair 1977). In adult buffalo we used tooth wear as an indicator of age, by measuring the height of incisor 1. Incisor-1 height declines by ~1 mm/yr in this population (A. E. Jolles, *unpublished data*). In 2001, pregnancy tests of 285 females were performed rectally by veterinarian Dave Cooper.

The data presented in this paper were collected during the dry seasons of 2000 and 2001. We tested a total of 1180 buffalo for bTB. Tested buffalo were drawn from three distinct subpopulations, centered in different areas of the park, Masinda, Nqumeni, and Manzibomvu sections. In 2000, 257 buffalo were tested for TB in Masinda section, in the southeastern part of the park. In 2001, 254 animals were tested in the centrally located Nqumeni section, 537 were tested in Masinda section, and 132 buffalo were tested in Manzibomvu section in the north of the park. The three 2001 capture sites accessed distinct buffalo subpopulations.

Necropsy methods and disease severity

Postmortem exams of TB-positive buffalo were conducted by park and State veterinarians on 225 buffalo culled due to positive TB-test results. Lungs, and lymph nodes of the head and respiratory system, as well as prescapular lymph nodes and the body cavity were checked for macroscopic TB lesions. In a subset of cases, *Mycobacterium bovis* was grown in culture to confirm pathogen identity and infection status. Each examined organ was rated for TB severity on a scale of 0–4, with 0 indicating that no lesions were found, 4 indicating that half or more of the organ was filled with TB lesions, and severity classes inbetween these

extremes indicating intermediate numbers and sizes of lesions. An overall disease-severity rating was derived from the combined ratings for all organs. Buffalo with the highest severity rating of 4 overall were those that the veterinarians judged would have died from TB within a year. This judgement was based on the majority of at least one lung lobe being occupied by TB lesions, severely impairing respiratory function. In addition, class-4 cases were always characterized by large TB lesions that were widespread throughout the body, strongly suggesting that the animal was not able to control the progression of lesions at that stage.

Modeling approach

We used an age-structured matrix population model to translate TB impacts on vital rates to disease effects on population growth rate and age structure. The population growth rate, λ, is given by the dominant eigenvalue of the Leslie projection matrix; the stable age distribution is given by the corresponding eigenvector, scaled to add up to 1 (Caswell 2001).

Age-specific mortality rates for healthy buffalo were derived from the age structure of herds with very low TB prevalence (<10%; average herd pervalence 5.5%); fecundity rates for healthy cows are based on pregnancy tests of TB-negative animals only (Jolles 2004). To obtain vital-rate parameters for infected animals, we adjusted these baseline parameters according to the estimates of disease effects detailed in this paper (Table 1). Population-wide parameters were then obtained by weighting healthy and infected vital-rate parameters according to disease prevalence. We treat the distribution of infection across different age classes as independent of herd TB prevalence. The available data from high- and low-prevalence herds support this assumption: In our model, TB affects vital rates of buffalo

aged 4.5 yr and older. For these age classes, age-specific TB prevalence is a linear function of herd TB prevalence (Appendix A).

To evaluate the effects of chronic disease on population growth rate and age structure in the general case, we used the same basic projection matrix as in the model for healthy buffalo above, but allowed the proportionate fecundity and adult survival reduction in infected individuals to vary between 0 and 1 or 0.4, respectively. Larger survival reductions are not presented here, since, by definition, a chronic disease does not kill most of its hosts quickly. We measured detectability of disease via changes in population age structure as the minimum TB prevalence at which the age structure of an infected population differs significantly from that of a healthy population. Statistical significance was established for each pair of parameter values (fecundity reduction and survival reduction), using chi-square tests, and assuming a sample size of 500 animals each in the modeled healthy and infected populations. We chose this as our reference sample size, because 1000 animals is about the maximum one might catch in the field per capture season. Thus, differences in population age structure that we label "detectable" could indeed be detected in the field, given the best possible capture effort. We programmed our models using Mathematica 5.0 software (2003; Wolfram Research, Champaign, Illinois, USA).

RESULTS

Effect of TB on mortality

Our estimate of disease mortality is based on the proportion of TB-positive animals that necropsy revealed to be in critical condition from the disease. Most cases of TB in the buffalo were mild (Fig. 1). Of the infected animals 65–75% (severity classes 0 and 1, some in 2) probably showed no clinical symptoms when alive, reflecting the slow progression of this chronic disease. Severe cases of TB that would likely have been fatal within a year were seen in 5% of TB-positive animals. All were adults, except for one 3-yr-old, indicating that disease mortality primarily affects adults. Of infected adults ($N = 92$ individuals), we judged 11% to have been in critical condition, yielding an estimate of 11% (95% confidence interval: [5.3%, 19.1%]) annual mortality from TB.

However, if TB mortalities were concentrated in old, moribund animals, our pathology findings need not indicate higher overall mortality rates: TB might simply be replacing malnutrition or diseases associated with old age as the proximate cause of death. To test this possibility, we examined whether older adults were more likely to be infected with TB than younger adults, and found this not to be the case (see Appendix B: Table B1). Further, among infected adults, we found no evidence that more severe TB infections were concentrated in older adults (see Appendix B: Fig. B1).
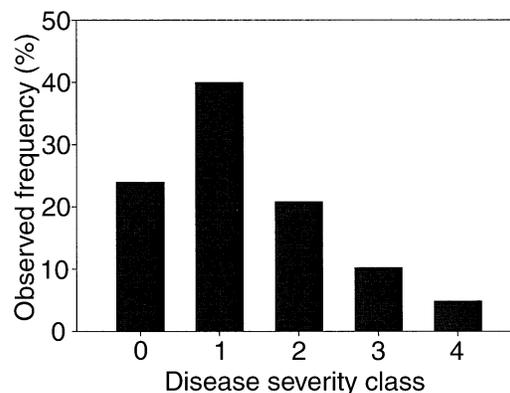

FIG. 1. Disease severity in TB-positive buffalo, all capture sites, year 2001. Disease severity classes are defined as follows: 0, no macroscopic lesions; 4, imminently fatal; 2 and 3, intermediate number and size of lesions.

Finally, TB-positive adult buffalo were younger than TB-negative adults from the same herds (Mann-Whitney U test; $N_{TB-} = 187$; $N_{TB+} = 137$; $P = 0.041$), confirming a higher mortality rate in infected animals. The latter data come from herds caught in Masinda section only, because TB prevalence was not high enough in Nqumeni and Manzibomvu sections to yield meaningful sample sizes of TB-positive adults to compare with TB-negative ones. The age pattern is robust to removing all animals that had previously been captured, to control for possible effects of the test-and-cull program on adult age distribution (Mann-Whitney U test; $N_{TB-} = 119$; $N_{TB+} = 106$; $P = 0.001$). These results corroborate our finding that TB increases mortality risk in adult buffalo.

Effect of TB on fecundity

When comparing subpopulations with low (2.2%, Nqumeni section) and high (53.3%, Masinda section) TB prevalence in 2001, we observed that the calf:cow ratio appeared higher for the low-prevalence area ($N_{lowTB} = 81$ cows, ratio = 0.64; $N_{highTB} = 170$ cows, ratio = 0.52; chi-square test: $\chi^2 = 3.13$; $P = 0.077$), suggesting an effect of TB on fecundity. To discover whether there was more direct evidence for a disease effect on fecundity in buffalo, we examined data from 285 females that were tested for both pregnancy and TB infection. We used multiple logistic regression, considering the following factors that might affect pregnancy status: area of origin, month when tested for pregnancy, age, and TB status. Statistically significant effects were found for test month, with more pregnancies detected later in the year when fetuses are of more advanced gestational age ($P < 0.001$); and TB status, with TB-positive females having lower pregnancy rates than uninfected females ($P = 0.018$; Appendix C: Table C1). We used late-season pregnancy data (Appendix C: Table C2) to quantify the reduction in fecundity due to TB. Infection does not appear to affect pregnancy

TABLE 2. Age distribution of observed and modeled buffalo populations with high and low TB prevalence.

Age (yr)	Observed subpopulations		Modeled population	
	<10% TB†	53% TB‡	0% TB	60% TB
0–1	13.7	11.6	13.7	12.9
1–5	36.8	38.7	34.4	35.2
5–9	18.5	16.9	16.0	18.0
9–15	23.5	25.3	26.1	26.2
16+	7.5	7.5	9.8	7.7

Notes: Comparisons between age distributions were made using chi-square tests, assuming a sample size of 500 buffalo for modeled populations. There are no statistically significant differences between any of the population age distributions.
  † N = 506 buffalo.
  ‡ N = 498 buffalo.

rates in young adult females (6–8 yr), but does affect subadults and older adults (≤5.5 yr and 9–16 yr old; N = 60; chi-square test: χ^2 = 5.65; P = 0.017). In affected age groups, TB reduced pregnancy rates by 27%—though this estimate of fecundity reduction due to disease carries substantial uncertainty as a result of the relatively small sample sizes. Senescent females (≥17 yr; N = 4 animals) have been included in this estimate, since there is no a priori reason to expect them to be more resilient to TB than the younger age groups.

Effect of TB on population growth rate and age structure

Elasticity analysis (Caswell 2001) of the buffalo population model shows that population growth rate responds most sensitively to changes in adult survival, and less to fecundity (Jolles 2004), as is typical of long-lived, slow-maturing animals with low fecundity (Heppell et al. 2000). As a result, TB affects population growth rate primarily through reducing adult survival, and to a lesser degree through impairing fecundity. The effects of TB prevalence on growth rate are both direct, in terms of immediate effects on the mean fecundity and survival, and indirect, through shifts in the age structure that would weight some classes more heavily than before. However, because the effects on age structure turn out to be minimal, the primary effects are direct reflections of the per capita losses (fecundity impairment and adult disease mortalities) due to TB. Thus, to a good approximation the growth rate, λ, decays linearly with disease prevalence P: $\lambda = 1.0404 - 0.0802 \times P/100$.

In contrast to growth rate, population age structure is not materially affected by TB, either in the data or in the model simulations. This can be seen by comparing the age structures of high (53%) and low (<10%) TB subpopulations within the park, or by examining the model simulations for uninfected and infected (60%) populations (Table 2). In the buffalo model, there are a variety of combinations of modified parameters that lead to minimal changes in age structure. In Fig. 2 we plot the minimum disease prevalence needed to cause detectable change in population age structure; the result is an off-center, hump-shaped response surface. The humped part of the response surface defines a range of vital-rate parameter combinations where disease effects on fecundity and survival compensate eachother's impacts on population age structure: moderate (8–20%) reductions in survival are hardest to detect in combination with fairly severe (20–60%) reductions in fecundity. In other areas of the response surface, compensation is less important. For example, moderate (<30%) fecundity reductions on their own do not result in detectable effects on age structure, and survival reductions in excess of 20% are easy to detect across the whole range of fecundity parameters. The disease-effect parameters observed for TB in buffalo—a reduction in fecundity by 27% and adult survival by 11%—fall within the response-surface's peak; that is, these effects on buffalo vital rates compensate each other's impacts on age structure to such an extent that even at 100% prevalence TB has no significant effect on population age structure.

DISCUSSION

Individual-level effects of TB

Most TB cases in buffalo were mild, with ~70% of infected animals examined postmortem unlikely to have shown symptoms of disease while alive. This finding is consistent with the expectation that *Mycobacterium bovis* typically causes chronic infections, which
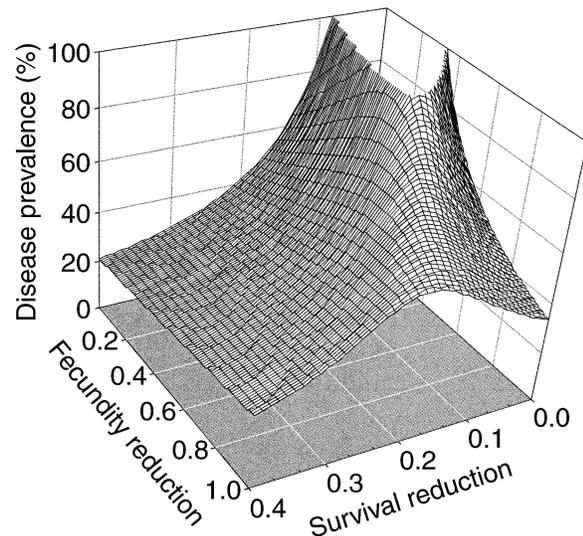

FIG. 2. Response of population age structure to simulated diseases, with varying impacts on adult survival and fecundity. The *x*- and *y*-axes represent the proportionate reduction in fecundity and survival, respectively, in infected individuals. The *z*-axis denotes the minimum disease prevalence at which the age structure of an infected population differs significantly from that of a healthy population.

can persist for many years in long-lived hosts before advancing to acute illness. Our estimate of 11% annual mortality risk due to the disease represents a substantial increase in mortality risk for adult buffalo, given high annual survivorship (95–99%) in the absence of disease (Sinclair 1977, Jolles 2004): Healthy 5-yr-old buffalo have a life expectancy of an additional 11 years, whereas infected 5-yr-olds may only live for another 6 years, on average, given this estimate of added mortality risk. TB also affected fecundity in buffalo, reducing pregnancy rates in infected females of most age groups by ~27%. There may be an interaction between the effect of TB on pregnancy rates and age of the infected cows. More data will need to be collected to clarify how cow age affects the impact of TB infection on fecundity.

Population-level effects of TB

Our models suggest that population growth rate may be reduced as a result of TB infection in buffalo. The magnitude of this effect scales essentially linearly with TB prevalence in the population. While there is of course some uncertainty in the exact age-specific vital rates for healthy and infected buffalo, which determine model output on population growth rate, these results are qualitatively very robust: TB clearly affects adult survival in buffalo, which is the vital rate that population growth rate is most sensitive to. Under the simple linear model, λ drops below 1 at 51% TB prevalence. However, it should be noted that in reality the threshold disease prevalence for negative population growth is likely to vary with buffalo population size, and will depend on the way in which density dependence and disease effects interact. Since TB only reduces population growth rate below unity at very high prevalences, we would not usually expect to see a population decline due to the disease. However, because of their lower growth rate, infected populations are expected to have difficulty recovering from any additional disturbances that may reduce their numbers. Our field data and model output also show that TB is unlikely to cause detectable changes in buffalo population age structure. The reason is clear from the regression given earlier for growth rate: for the observed elasticities, even a 50% TB prevalence would result in a shift in abundance of successive age classes of less than 2%, making detection of age-structure shifts problematic. This is compounded by the fact that fecundity impairments due to disease tend to shift the age distribution towards older animals, whereas increased adult mortality counteracts this bias. The main effect of TB on the population is thus a sharp reduction in population resilience.

Conclusions

TB in buffalo presents a management dilemma: on the one hand, population-level effects of the disease are hard to detect. TB does not cause conspicuous mass mortalities, nor alter population age structure, even at high prevalence. And, in the absence of other disturbances, TB is unlikely to affect population size. On the other hand, TB does appear to have the potential to reduce population growth rate, and therefore resilience to disturbance, considerably. As a result, TB is unlikely to be identified as a problem for buffalo populations until adverse circumstances reduce population size and a population fails to recover at the rate expected in the absence of disease. At that point, the situation will not be easily mitigated, as controlling diseases is difficult and costly once high prevalences have been reached.

This syndrome of poor detectability coupled with strong effects on population resilience may not be limited to TB, or to buffalo. The characteristics that drive the syndrome—moderate disease impacts on adult mortality and fecundity, host population growth rates that are sensitive to changes in adult survival and not too high in the first place—typify many chronic diseases and large animal hosts. In these systems, typical warning signs that disease is modifying host population dynamics, specifically changes in population size and age structure or sudden mass mortalities, may not be present despite large effects on population growth rate. This has clear implications for wildlife disease management. There appears to be no substitute for monitoring individual-level effects of disease on host vital rates in order to decide, in a timely manner, whether intervention to control a chronic disease is merited.

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APPENDIX A

Data supporting the assumption that the distribution of TB infection across age classes is independent of herd TB prevalence are available in ESA's Electronic Data Archive: *Ecological Archives* E086-124-A1.

APPENDIX B

Data corroborating mortality effects of bovine TB in adult African buffalo are avilable in ESA's Electronic Data Archive: *Ecological Archives* E086-124-A2.

APPENDIX C

Data on bovine-TB effects on fecundity in African buffalo are available in ESA's Ecological Data Archive: *Ecological Archives* E086-124-A3.