

Novel coupling of individual-based epidemiological and demographic models predicts realistic dynamics of tuberculosis in alien buffalo

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Summary

1. Increasing sophistication of population viability analysis has broadened our capacity to model population change while accounting for system complexity and uncertainty. However, many emergent properties of population dynamics, such as the coupling of demographic processes with transmission and spread of disease, are still poorly understood.

2. We combined an individual-based demographic (VORTEX) and epidemiological (OUTBREAK) model using a novel command-centre module (METAMODEL MANAGER) to predict the progression of bovine tuberculosis in introduced swamp buffalo *Bubalus bubalis* in northern Australia and validated the model with data from a large-scale disease-monitoring and culling programme. We also assessed the capacity to detect disease based on incrementing sentinel (randomly sampled individuals) culling rates.

3. We showed that even high monitoring effort (1000 culled sentinels) has a low (< 10%) probability of detecting the disease, and current sampling is inadequate.

4. Testing proportional and stepped culling rates revealed that up to 50% of animals must be killed each year to reduce disease prevalence to near-eradication levels.

5. Sensitivity analysis indicated that prevalence depended mainly on population demography (e.g. female age at primiparity) and the additional mortality induced by disease, with only minor contributions from epidemiological characteristics such as probability of transmission and encounter rate. This is a useful finding because the disease parameters are the least well known.

6. *Synthesis and applications.* Our models suggest that details of population demography should be incorporated into epidemiological models to avoid extensive bias in predictions of disease spread and effectiveness of control. Importantly, we demonstrate that low detection probabilities challenge the effectiveness of existing disease-monitoring protocols in northern Australia. The command-centre module we describe linking demographic and epidemiological models provides managers with the tools necessary to make informed decisions regarding disease management.

Key-words: *Bubalus*, disease, invasive species, METAMODEL MANAGER, OUTBREAK, population viability analysis, VORTEX

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Introduction

Population viability analysis models have become increasingly sophisticated over the last 20 years, with both flexible but generic software packages (e.g. RAMAS and VORTEX) (Lacy 2000; Akçakaya 2009) and specialized or species-specific programs incorporating algorithms that target particular demographic or genetic questions (e.g. Miller & Lacy 2003a; Keith *et al.* 2008; Fordham *et al.* in press). Despite this evolution in the development of applied demographic models, many important components affecting population dynamics are not modelled effectively within typical population viability analysis applications (but see the studies by Haydon, Laurenson & Sillero-Zubiri 2002; Haydon *et al.* 2006). One such component is infectious disease and its transmission dynamics which affect, and are in turn affected by, the structure of the host population. Similarly, most epidemiological models focus primarily on the disease status of the individuals in the population (i.e. susceptible, infected, recovered) and assume either static population size and structure, or use only simple models of population change (e.g. Barlow 1995; Bradshaw & Brook 2005; Calvete 2006; Craft *et al.* 2011). Such models therefore estimate morbidity and mortality rates without considering the important effects of random demographic, environmental and genetic factors.

To address the limitations of existing approaches, a more explicit coupling of stochastic and age-/sex-structured demographic and epidemiological models is required. However, this is generally complicated by the different time-scales over which the processes of population turnover and disease dynamics operate; the former is most often modelled as processes occurring between approximately annual reproductive events and the latter typically over finer temporal scales (e.g. daily or weekly). Individual- or agent-based models offer particular advantages in this regard (Grenfell & Dobson 1995) because they explicitly assign fitness states to individuals throughout their lifetime, allowing the dynamics of disease transmission to be captured with more realism. Here we describe a novel software application for coupling two individual-based models, each designed specifically to portray stochastic demographic/environmental and epidemiological processes. We apply the linked model structure to an example system in northern Australia to describe the temporal dynamics of tuberculosis spread and control in a free-ranging population of feral swamp buffalo *Bubalus bubalis* (Linnaeus).

Swamp buffalo were introduced in small numbers as live-stock to the seasonal tropics of northern Australia in 1826 and 1827, and again in 1843 from South East Asia (Letts 1962; McMahon *et al.* 2011), but were soon released or escaped and subsequently spread throughout the Northern Territory (McMahon *et al.* 2011). The feral population grew rapidly to around 350 000 by the 1960–1970s (Freeland & Boulton 1990). The detection of tuberculosis in the Australian buffalo population and the national cattle herd, and a desire to eradicate the disease from Australian livestock, led to a broad-scale ‘Brucellosis-Tuberculosis Eradication Campaign’ (BTEC) in the 1980–1990s (Radunz 2006), which successfully reduced or

eradicated buffalo from pastoral lands (McMahon *et al.* 2011). Since then, the buffalo population has slowly recovered (Bradshaw *et al.* 2007) and spread to previously eradicated areas, although a regular tuberculosis-monitoring programme has not yet detected tuberculosis in the recovering population (Animal Health Australia 2009).

Although the tuberculosis bacterium *Mycobacterium bovis* has occasionally been detected in Australian species other than cattle and swamp buffalo, the last cases in Australian domestic cattle were detected in 2000. The disease is also currently widespread in Africa, southern Europe, the Middle East and parts of Asia, and is an economic burden in many of these regions (Michel, Müller & van Helden 2010). However, no one has yet empirically evaluated the dynamics of a reintroduction of the disease in the recovering buffalo population in Australia, nor estimated the probability of detecting the disease during regular monitoring. This gap in knowledge has serious implications for future disease control should an outbreak occur. Considering the original infection in Australian buffalo was most likely from cattle transported to the north from the south east of the country (Cousins & Roberts 2001), and that transmission occurs primarily via aerosols of saliva and urine among and within species, it is important to assess the dynamics of the disease in remote regions of Australia where free-ranging cattle and buffalo regularly mix (McMahon & Bradshaw 2008). As such, Australia stands to gain much by having an empirically guided plan to control the disease should it re-emerge, especially considering the remoteness of many bovid population disease reservoirs that might elude detection for years (Bradshaw *et al.* 2007). Presenting a novel software application that explicitly links individual-based epidemiological and demographic models, we (i) model the rate of spread of tuberculosis in the wild swamp buffalo population from three different initial states of prevalence, (ii) evaluate the probability of detecting the disease from samples of randomly culled individuals during routine surveillance by quarantine authorities, and (iii) determine the culling rate necessary to suppress the disease to near-zero prevalence should an outbreak occur. Our goal is to show the importance of considering the complexity of the demographic–epidemiological linkages for predicting disease dynamics and control efficiency using Australian buffalo as a case study.

Materials and methods

OUTBREAK

Epidemiological model description

We used the software package OUTBREAK (<http://www.vortex9.org/outbreak.html>) that simulates disease dynamics under an epidemiological base model incorporating susceptible, exposed, infectious and recovered individuals (Anderson 1982; May 1986). The prevalence of infectious disease in wildlife populations depends on the number of individuals already infected, as well as on the numbers of susceptible and exposed individuals. To model infectious processes, the state of

each individual in the population is tracked (on a daily time step), and the probabilities of transition among states are specified as functions of the number of individuals currently in each state and of other relevant parameters such as contact rate and the latent period of infection. Multiple iterations of a given data set are used to generate mean population characteristics as outputs.

OUTBREAK defines five states for individuals: (i) pre-susceptible, (ii) susceptible, (iii) exposed, (iv) infectious and (v) recovered. The *pre-susceptible* state includes all individuals in the latency period from birth to earliest age of susceptibility that are not susceptible to disease because of either maternal immunity or lack of disease exposure. *Susceptible* individuals are capable of contracting the disease given exposure and later becoming infectious. This state determines whether and how a susceptible individual is exposed and becomes infectious. This can occur either by encountering an infectious conspecific in the same population, or by contact with an outside disease source (e.g. from another species). *Exposed* (and *infected*) (Barlow *et al.* 1997) individuals are those that have encountered an infectious individual and have contracted the disease-causing agent but have not yet become infectious. The residence time in this state represents the incubation period. Individuals that are exposed but never become infectious (i.e. infected but never actively shed the pathogen responsible for the disease) remain in the exposed state. *Infectious* individuals, also sometimes known as *diseased* in the bovine tuberculosis literature (Barlow *et al.* 1997), are those actively shedding the disease organism and are therefore capable of transmitting to another individual. An infectious individual can remain permanently infectious, recover without immunity, recover with immunity, or die. *Resistant* individuals are those that cannot be infected again or develop disease because of immunity acquired from a previous infection or vaccination. These individuals can remain resistant for the duration of their life or return to a susceptible state. A detailed software description and all disease parameters used in the OUTBREAK model are described in Appendix S1 in Supporting Information, but we summarize them briefly here: encounter rate = 5 individuals/day, daily transmission probability = 0.00027, daily probability of encounter with outside (cattle) disease = 0.15, average prevalence in outside-source (cattle) individuals = 0.08, outside disease source encounter rate = $0.15 \times 0.08 = 0.012$, proportion of *infectious* individuals that remain so indefinitely = 0.425, minimum and maximum incubation period of infection = 150 and 2555 days, respectively, minimum and maximum time an animal can remain infectious = 60 and 6205 days, respectively. We also considered a density-dependent scenario where contact rate was set as the proportion (0.001) of the population an exposed/infectious individual encounters/day.

VORTEX

Demographic model description

Although OUTBREAK can incorporate basic demographic rates to project the diseased population through time (see Appendix S1, Supporting Information), it is more biologically realistic to link the epidemiological component to a full population viability analysis software program. Program VORTEX (Lacy, Borbat & Pollak 2010; <http://www.vortex9.org/vortex.html>) is an individual-based age- and sex-structured stochastic simulation (Miller & Lacy 2004) of the dynamics of small populations and the extinction process (Lacy 2000). The coupling of OUTBREAK and VORTEX is described in more detail below (see METAMODEL MANAGER). A detailed software description and all demographic parameters used in the VORTEX model are

described in detail in Appendix S1 (Supporting Information); however, here we give a brief summary.

We set initial population size at 5000 individuals, or approximately 5% of the 'true' current population size of 100 000 individuals. We set an arbitrary K at 15 000 individuals for the model, representing a 'true' K of 300 000 individuals (Freeland & Boulton 1990). Mortality rates were set according to average values calculated from life tables derived from culled individuals in the Northern Territory (Collier *et al.* 2011; McMahon *et al.* 2011). Maximum longevity for both sexes was set at 17 years, an age approximately 1% of offspring are expected to reach. Fertility was 0.90; to this, we added an arbitrary 0.02 SD. Neonate sex ratio is approximately even. We set a density-feedback function where fertility declines gradually to 0.70 at K . The proportion of adult males in the breeding pool was set at 0.36 (Tulloch & Grassia 1981). We invoked the observed relationship between generation length (7.8 years) and the occurrence of catastrophes for vertebrates (Reed *et al.* 2003) to simulate drought catastrophes ($c = 0.02$). When a drought was invoked, juvenile survival was reduced to 40% of its original values, rising to 90% of its original values by age 5, for one time step (year).

Demographic effects of disease

Tuberculosis is a major concern to the cattle industry because of its severe reduction in livestock productivity and export earnings (Bicknell, Wilen & Howitt 1999). However, the documented lethal or sublethal effects of tuberculosis on bovids are somewhat equivocal (Woodford 1982; Cross *et al.* 2009) because of the normally slow progression of this chronic disease (Jolles, Cooper & Levin 2005). Despite the observation that most infections in African buffalo *Syncerus caffer* are mild, Jolles, Cooper & Levin (2005) determined an overall increase in mortality risk of 11% and a decline in fertility by 27% in African buffalo based on field necropsy data and an age-structured population model. As such, we applied these reductions to the intercepts of the density-modified mortality and fertility relationships described in the demographic model for individuals in the *exposed* and *infectious* classes. We also applied an additional 10% reduction in the mortality rates incurred during a catastrophe to capture the likely higher susceptibility of sick individuals during poor-resource years.

METAMODEL MANAGER

To make an explicit, data-driven linkage between simulation models, we used a command-centre package, METAMODEL MANAGER (Miller & Lacy 2003b). METAMODEL MANAGER was developed as a tool for linking any number of simulation models, each representing a component of an overall system, by controlling the sequence of model steps and passing any shared data among the interacting simulations as they sequentially step through them (see a detailed software description in Appendix S1, Supporting Information). METAMODEL MANAGER has the added advantage of being able to account for temporal mismatch between demographic and disease models parameterized in VORTEX and OUTBREAK. VORTEX typically runs on an annual time step (although a 'year' can be modified according to the organism's particular life cycle), while OUTBREAK operates its epidemiological model on a daily time step (Fig. S1, Supporting Information). Although considerably more comprehensive and flexible, in this case we used METAMODEL MANAGER to call up an instance of OUTBREAK to simulate the disease dynamics and to pass relevant parameters to VORTEX to allow modification of population demographic rates as a function of an individual's disease state (Fig. S1, Supporting Information). In this way, an

individual's demographic behaviour can change each year during the population projection, as they are exposed to the infectious agent, contract the disease and experience reduced rates of survival and/or reproduction for that year. All other aspects of population dynamics unrelated to disease are controlled directly by VORTEX, and all simulations are spatially implicit (with only edge-contact probabilities considered).

PROJECTION SCENARIOS

Disease progression

We projected population scenarios for 100 years with initial tuberculosis prevalence values of 0%, 8% and 16% based on null, average and maximum prevalence estimates from BTEC (Radunz 2006). 'Prevalence' here refers to the combined proportion of *exposed* and *infectious* individuals in the population. We calculated mean prevalence each year from initial state using 250 stochastic iterations of the coupled model. We provide example computer code for VORTEX, OUTBREAK and METAMODEL MANAGER applications in Appendix S2 (Supporting Information).

Detection

The Australian Quarantine Inspection Service monitors wild buffalo populations for the re-emergence of tuberculosis and other wildlife diseases via random culling of sentinel individuals across northern Australia (Animal Health Australia 2009). Although skin and other tissue diagnostic tests have variable success at identifying the tuberculosis pathogen in live exposed and infected bovids (Mishra *et al.* 2005), the laboratory analysis of identified granulomas submitted postmortem is highly specific; during BTEC, the probability of failing to detect the disease if present varied between 1/10 000 and 1/50 000 (i.e. probability of detection if present = 0.99990–0.99998) (Radunz 2006).

We therefore assumed error-free identification of the infection if present in a sample, to be conservative, and used sample sizes of 10, 50, 100 and 1000 randomly culled buffalo. We estimated the probability of successful detection with a random binomial sampler implemented by function `rbinom` in the `R` Package (R Development Core Team 2011) for each cull level and based on the prevalence estimated for each projection averaged across all iterations. We are assuming that prevalence is known or estimated without bias. Here, we generated a random binomial prediction of the number of individuals identified with tuberculosis (x) from a sample of $n = 10, 50, 100$ or 1000 sentinel individuals tested based on that iteration's projected prevalence (p) for each year in the projection. When $x > 0$, a positive detection occurred (1); otherwise, detection = 0 for that iteration. We took the mean value of detections (vector of 0s and 1s) over all iterations as that year's overall probability of detection. We investigated two initial prevalence scenarios: (i) zero initial prevalence (with outside source as described previously) and (ii) 0.02% (0.0002) initial prevalence, which is the internationally recognized 'tuberculosis-free' limit (Barlow *et al.* 1997).

Culling

Given the previous success of broad-scale culling programmes to eradicate tuberculosis from diseased herds, we estimated the effectiveness over 15 years of simple proportional culls to reduce disease in herds with varying initial states of prevalence. Culls are handled via a customized modifier routine in METAMODEL MANAGER. We investigated two initial prevalence state scenarios: 0.08 and 0.0002, and six

proportional culling rates: 0.05, 0.10, 0.20, 0.30, 0.40 and 0.50. The first scenario (initial prevalence = 0.08) represents conditions emulating the population's disease state at the onset of the Brucellosis-Tuberculosis Eradication Campaign. For the scenario where initial prevalence = 0.0002, proportional culling began only when total prevalence exceeded 0.0002 in any time step. This scenario represents a modern-day situation where low prevalence is initially detected and then relatively modest culling is implemented whenever background prevalence is estimated to exceed 0.0002. We also considered a stepped culling regime with high initial (first year) proportional culling of 0.80 followed by a maintenance cull of 0.10 thereafter. Such stepped culling regimes tend to be more cost-effective than constant proportional culls (McMahon *et al.* 2010).

SENSITIVITY ANALYSES

We constructed a separate meta-model module to vary parameter inputs in both VORTEX and OUTBREAK simultaneously for a global sensitivity analysis (Naujokaitis-Lewis *et al.* 2009). To ensure sampled parameter values covered the entire range, we used Latin hypercube sampling (Iman, Campbell & Helton 1981) with 1000 samplings from realistic ranges of the following parameters: female age at primiparity, male age at sexual maturity, % males in the breeding pool, additional mortality risk from disease, SD of mortality risk across age groups, the (density-dependent) fertility function's intercept and value at K (VORTEX), probability of tuberculosis transmission, encounter rate, minimum and maximum incubation periods, and the probability of remaining infectious indefinitely (OUTBREAK). The values for each parameter were uniformly distributed. For each iteration of randomly selected parameter values, we projected the population 50 years and recorded the mean disease prevalence over 100 replicate projections.

We constructed a general linear model using prevalence (complementary log–log transformed) as the response and the varied parameters as fixed effects. The explanatory terms represent the demographic and disease characteristics of interest for sensitivity analysis, and their standardized coefficients indicate their relative influence on prevalence (McCarthy, Burgman & Ferson 1995). We considered the saturated, VORTEX parameter-only, OUTBREAK parameter-only, various themed two-effect (e.g. fertility function parameters only), all leave-one-effect-out and all single-effect models in the set (32 models in total) (Garnett & Brook 2007). We compared all models using the Bayesian information criterion (BIC) because Akaike's information criterion (AIC) favours more complex models when tapering effects exist and samples are large (and our simulation iterations are arbitrarily large), whereas BIC identifies the principal drivers of complex relationships within larger data sets (Link & Barker 2006). We assessed the strength of evidence for each model relative to the set based on relative model weights (w_{BIC}). To assess the relative explanatory power of each model for predicting prevalence, we calculated the % deviance explained. We also calculated the standardized coefficients (α_i/SE_i) for each term in the saturated model as a second relative metric of prevalence sensitivity to variation in vital rates (McCarthy, Burgman & Ferson 1995).

Results

POPULATION PROJECTIONS

A reference scenario based on 1000 iterations of the base stochastic population viability analysis model run in VORTEX

resulted in a simulated population that increased gradually over the 100-year projection, giving a stochastic intrinsic exponential rate of increase $r = 0.009$ and an annual variation in growth $SD(r) = 0.09$. The deterministic model gave a generation time of 5.66 and 8.53 for females and males, respectively, and an adult male/female ratio = 0.531. The stable-stage distribution (Fig. S2, Supporting Information) indicated the highest proportional abundance in the 0–1 year age class. The average population size across the 1000 iterations never reached K (set at 15 000) during the 100-year projection interval, but the population size stabilized at approximately 0.75 K after 70 years. This rate of increase appears to agree with the observed recovery of buffalo following BTEC.

DISEASE PROGRESSION

Starting with a zero initial disease prevalence in the buffalo population, tuberculosis was introduced from the external source (cattle) at the specified probability (0.012) and average prevalence steadily increased over the 100-year projection to approximately 0.05. Higher initial prevalence states steadily

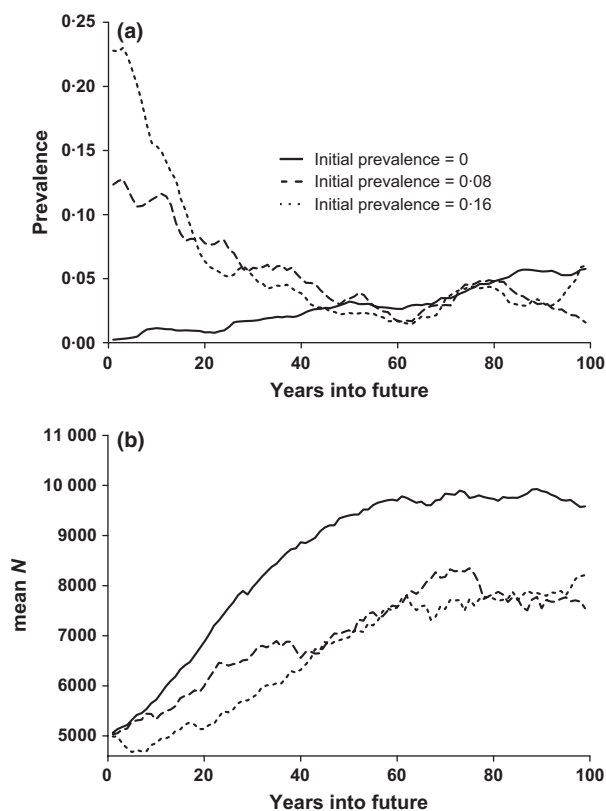


Fig. 1. (a) Mean progression of tuberculosis in a population of free-ranging swamp buffalo in northern Australia, based on a stochastic (250 iterations) epidemiological model (OUTBREAK) linked directly to an age- and sex-structured demographic simulation (VORTEX). Three initial prevalence values are shown (0, 0.08 and 0.16, including outside source – see Materials and methods). Total prevalence stabilizes to around 0.05 after approximately 80–100 years. (b) Mean total estimated total population size for each initial prevalence value over the 100-year projection.

declined to also stabilize around 0.05 after 100 years (Fig. 1a). Population size increased and then stabilized after approximately 60 years at around 10 000, 8000 and 7500 individuals for initial prevalence of 0, 0.08 and 0.16, respectively (Fig. 1b). When contact rate was set as a proportion of population size, prevalence trends were similar but stabilized at a higher expected prevalence (0.10) (Fig. S3a, Supporting Information); population size trends were similar using the density-dependent contact rate (Fig. S3b, Supporting Information).

DETECTION

With an initial prevalence of zero (but with the possibility of infection from an outside source), detection probability slowly increased over 15 years (Fig. 2). Detection probability was low (< 0.10) in all sampling regimes considered (10, 50, 100, 1000 culled sentinel individuals), and despite increasing as expected with greater sampling intensity, there was only a small increase in detection probability with more intensive sampling (Fig. 2a). Initiating the population with a 0.0002 prevalence value resulted in no obvious increase in detection probability over the 15-year interval (Fig. 2b). However, detection probability increased to a maximum of nearly 0.20 with an annual sample of 1000 culled sentinel individuals and averaged approximately 0.10 over all sampling intensities considered (Fig. 2b). We also constructed a simple deterministic Reed-Frost model with no demographic structure as comparison using the same parameters as in OUTBREAK to determine whether the disease could be detected (see Appendix S1, Section 3 in Supporting Information). Indeed, detectable disease was established after 10 years at a low but stable rate of 0.0004 (two of 5000 individuals).

CULLING

Over the 15-year management interval, an initial 0.08 prevalence was not suppressed to near-zero with a proportional culling rate of approximately < 0.30 assuming either a fixed (Fig. 3a) or proportional contact rate (Fig. S4, Supporting Information). The decline in prevalence tracks the reduction in population size at the various culling rates (Fig. 4). This rate of decline agrees well with phenomenological models of spatial buffalo population dynamics, which predict 95% reduction in the total population size (i.e. both healthy and diseased animals) after 10 years with a proportional cull of 0.30 (McMahon *et al.* 2010). A proportional culling rate ≥ 0.40 eradicated the disease after only 4 years (Fig. 3a). A stepped culling regime (0.80 initially followed by 0.10 maintenance thereafter) gave a final prevalence (~ 0.02) similar to that arising from the constant proportion cull of 0.20 (Fig. 3a). These projections closely mimic the decline in prevalence observed during BTEC; indeed, the number of infected individuals per million cattle at risk declined to near-zero after 10 years of intensive culling (Cousins & Roberts 2001) (Fig. S5, Supporting Information).

A more risk-averse management programme, where proportional annual culling was implemented whenever the actual

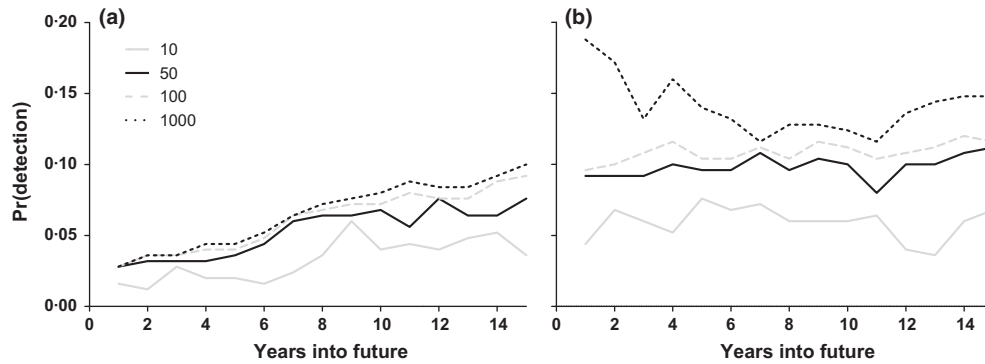


Fig. 2. Probabilities of detecting tuberculosis in an increasing sample of culled sentinel individuals (10, 50, 100 and 1000) with an initial prevalence of (a) zero (outside disease source only) and (b) 0.02%, forecast for 15 years.

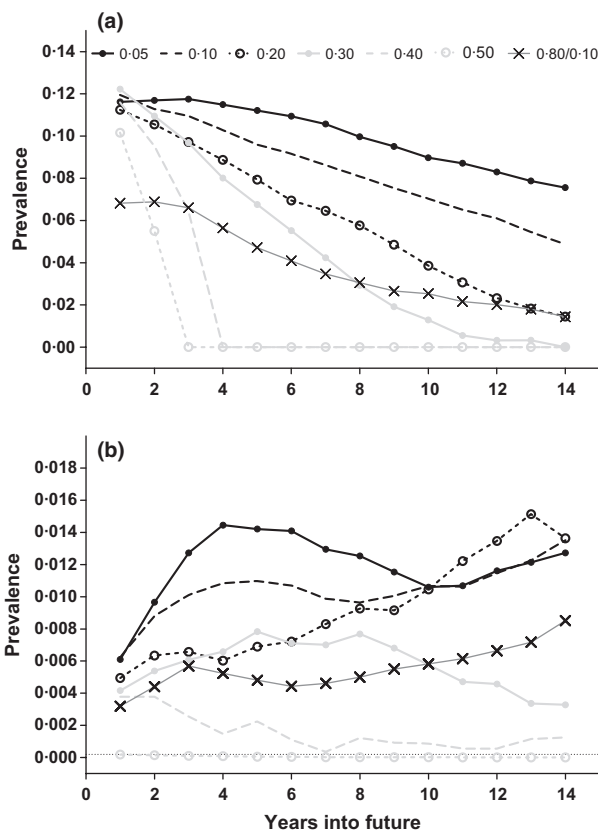


Fig. 3. Predicted reduction in tuberculosis prevalence in free-ranging Australian swamp buffalo at various proportional culling rates (i.e. proportion of total population culled in each year from 0.05 to 0.50). Initial prevalence was set at (a) 0.08 and (b) 0.02%; the latter scenario invoked culling only when total disease prevalence was greater than or equal to the internationally recognized 'tuberculosis-free' prevalence of 0.02%. The final proportional culling regime (0.80/0.10) indicates a 0.80 initial (Year 0) cull followed by a 0.10 maintenance cull thereafter.

background prevalence exceeded 0.0002 (0.02%, and starting with 0.02% prevalence in the population), suggested that suppression (i.e. keeping prevalence near or below 0.02%) of the disease was not achieved until a constant proportional culling rate of at least 0.50 (Fig. 3b). Indeed, all proportional culling

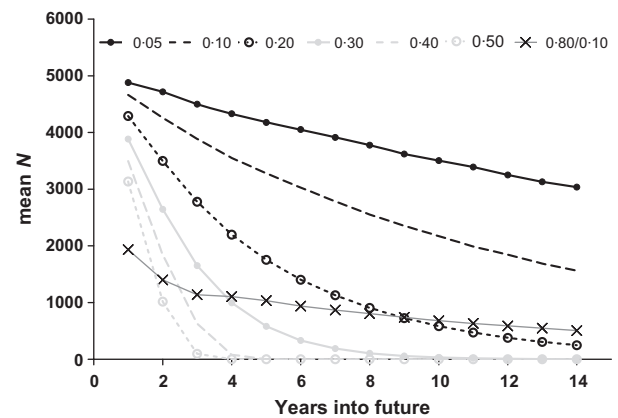


Fig. 4. Predicted trajectory of the free-ranging Australian swamp buffalo population at various proportional culling rates (i.e. proportion of total population culled in each year from 0.05 to 0.50). Initial tuberculosis prevalence was set at 0.08, and the final proportional culling regime (0.80/0.10) indicates a 0.80 initial (Year 0) cull followed by a 0.10 maintenance cull thereafter.

rates ≤ 0.20 were not even successful at reducing prevalence over the 15-year programme, neither was the stepped 0.80/0.10 culling regime (i.e. infection rate outpaced culling; Fig. 3b). Of course, the probability of detecting such low disease prevalence would be, in fact, much lower than the 0.0002 threshold used here; however, it demonstrates that this sort of approach is unlikely to be realistic in terms of both monitoring and prevalence reduction once a disease was established and detected.

SENSITIVITY

The demographic (VORTEX) parameters generally had a much larger influence on final disease prevalence than did the epidemiological (OUTBREAK) parameters (Table 1). Female age at primiparity was overwhelmingly the most influential parameter, with younger breeding leading to higher overall prevalence (Table 1). The additional mortality incurred from tuberculosis, and the low-density fertility values had the next highest influence on prevalence. Considering the OUTBREAK parameters alone, the probability of transmission had the highest influence, followed by encounter rate, minimum incubation time,

Table 1. Global sensitivity analysis contrasting 32 general linear models examining the relative influence of 12 demographic and disease parameters on tuberculosis prevalence

Model	<i>k</i>	<i>LL</i>	Δ BIC	wBIC	%DE	α_n/SE_n	$st \alpha_n/SE_n $
$\sim tr + en + min + max + F + M + mb + mm + msd + N90 + N70$	12	-524.83	0.000	0.255	85.83	-	-
$\sim tr + en + min + max + r + F + M + mb + mm + msd + N90$	12	-524.85	0.05	0.249	85.83	-	-
$\sim tr + en + min + max + r + F + M + mm + msd + N90 + N70$	12	-524.94	0.22	0.229	85.83	-	-
$\sim tr + en + min + r + F + M + mb + mm + msd + N90 + N70$	12	-525.18	0.71	0.179	85.82	-	-
⋮							
Saturated	13	-524.81	6.88	0.008	85.83	-	-
VORTEX parameters only	9	-547.72	18.15	<0.0001	85.17	-	-
⋮							
OUTBREAK parameters only	6	-1498.19	1905.27	<0.0001	0.75	-	-
$\sim F$	2	-1249.11	1379.48	<0.0001	39.69	-51.08	1.000
$\sim mm$	2	-1333.14	1547.55	<0.0001	28.66	-43.69	0.855
$\sim N90$	2	-1399.46	1680.20	<0.0001	18.54	35.36	0.692
$\sim tr$	2	-1501.63	1884.53	<0.0001	0.07	4.64	0.091
$\sim en$	2	-1500.54	1882.35	<0.0001	0.29	4.48	0.088
$\sim msd$	2	-1501.63	3023.99	<0.0001	0.07	-2.57	0.050
$\sim min$	2	-1501.53	1884.34	<0.0001	0.09	2.06	0.040
$\sim M$	2	-1500.91	1883.10	<0.0001	0.21	1.92	0.038
$\sim max$	2	-1501.89	1885.05	<0.0001	0.02	-0.85	0.017
$\sim mb$	2	-1501.96	1885.18	<0.0001	<0.01	0.49	0.010
$\sim N70$	2	-1501.81	1884.89	<0.0001	0.03	0.28	0.006
$\sim r$	2	-1500.64	1882.56	<0.0001	0.26	-0.16	0.003

Models ranked according to Bayesian information criterion (BIC) weights (wBIC); the top section of the Table shows the 4 most highly ranked models accounting for over 99% of the combined wBIC; the bottom section lists the single-term models only. Shown are the number of model parameters (*k*), minimum negative log-likelihood, difference between the top-ranked model's BIC and that of the current model (Δ BIC) and the % deviance explained (%DE). Alongside each single-term model, the standardized coefficients (α_n/SE_n) for each term appearing in the saturated model are given, and the calibrated (to max = 1) absolute standardized coefficients ($st|\alpha_n/SE_n|$). The relative importance of the terms on final disease prevalence is shown by both the magnitude of the %DE of the single-term models and the standardized coefficients for each term from the saturated model.

VORTEX parameters: *F* = female age at primiparity, *M* = male age at sexual maturity, *mb* = % males in the breeding pool, *mm* = additional mortality risk from disease, *msd* = SD of mortality risk across age groups, *N90* = fertility function's intercept, *N70* = fertility function's value at *K*.

OUTBREAK parameters: *tr* = probability of tuberculosis transmission, *en* = encounter rate, *min* = minimum incubation period, *max* = maximum incubation period, *r* = probability of remaining infectious indefinitely.

maximum incubation time, and finally, the probability of remaining infectious, but the overall deviance explained by any OUTBREAK parameter was low compared with those from VORTEX (Table 1). These results, and a comparison between the fully coupled model and an OUTBREAK-only (simplified demography) simulation (Fig. S6, Supporting Information), demonstrate that population dynamics are the major determinants of disease dynamics in a population.

Discussion

The novel, 'real-time' interconnection of individual-based epidemiological and demographic models that necessarily operate at different temporal scales is a major advance in ecological disease modelling. This will help to identify more efficient monitoring programmes and equip disease-control authorities with an empirically based target for intervention (either vaccination or culling, as required). An essential element in this system is the command-centre software METAMODEL MANAGER, which provides the platform through which different models can communicate (Fig. S1, Supporting Information). In the buffalo example developed, we combined epidemiological and demographic models; however,

there is virtually no limitation to expanding the number of different models in the framework. For example, separate demographic models could be combined in multispecies interactions (e.g. predators and prey, hosts and parasites, competitors), biophysical models (such as vegetation or climate change predictions) could inform demographic inputs, or more advanced spatial elements that take metapopulation structure and spatio-temporal variability in habitat suitability into account (e.g. Akçakaya 2009; Brook *et al.* 2009) could all improve predictive capacity, biological reality and management effectiveness.

The practical implications of the swamp buffalo example for tuberculosis monitoring and management are manifold. Our long-term (100 years) and management-relevant (15 years) predictions appear to follow previously observed tuberculosis dynamics in free-ranging bovinds. We have confirmed that although the rate of bovine tuberculosis build-up is slow, it can increase rapidly when demographic rates and transmission probabilities are high. We therefore reiterate previous calls to reduce buffalo densities across much of their current range (Bradshaw *et al.* 2007; McMahon *et al.* 2010), not only to minimize the direct ecological damage that high densities elicit (Bradshaw *et al.* 2007),

but also to minimize the risk of disease re-emergence and reduce its rate of spread.

A corollary of this work is that the apparent eradication of tuberculosis from Australian buffalo following BTEC in the 1990s (Radunz 2006) is no reason to relax disease-monitoring and risk-management plans. Indeed, we have shown that even relatively large (1000 individuals) sentinel culling samples still suffer from a low (< 0.10) probability of disease detection, even assuming complete disease-screening detection. The normally low prevalence and slow progression of tuberculosis in wild populations suggest that a more strategic sampling protocol is required; for example, we recommend more intensive sampling in areas of higher relative density, or in locations where contact with potential external sources are most likely (e.g. with free-ranging livestock at water holes).

We found that a high (0.40) proportional culling regime is required to eradicate the disease once established (average prevalence = 0.08). Even with such apparently low prevalence compared with bovids in other regions of the world such as African buffalo (Jolles, Cooper & Levin 2005), eradication to near-zero prevalence requires ≥ 10 years of intensive, population-wide culling. This would be likely to be prohibitively expensive given that BTEC cost about AU\$850 million to implement, which equates approximately to US\$1.7 billion in 2010-equivalent value (data from McCormick 2001; Frawley 2003). However, this expense does not include the likely opportunity costs of the disease to the Australian livestock export markets: the Australian government estimates that an uncontrolled outbreak of a virulent livestock disease such as foot-and-mouth in Australia '... could lead to key beef, lamb and pork export markets being closed for more than a year; control costs would be between \$8 billion and \$13 billion, and the consequences of an outbreak would be felt for up to 10 years' (Productivity Commission 2002). Of course, the effectiveness of culling can be improved with fine-scale spatially explicit models (e.g. McMahon *et al.* 2010) that take regional variation in prevalence and localized habitat suitability into account.

Other limitations include some uncertainty in model parameters, especially epidemiological rates such as transmission probability, contact rate and latency period (McClintock *et al.* 2010). Fortunately for this particular example, there are ample vital rate estimates (McMahon *et al.* 2011) and measures of bovine tuberculosis epidemiology (McCool & Newton-Tabrett 1979; Woodford 1982; Neill *et al.* 1988, 1989, 1992; Barlow *et al.* 1997; Menzies & Neill 2000; Cousins & Roberts 2001; Jolles, Cooper & Levin 2005; Radunz 2006; Cross *et al.* 2009). It is also encouraging that the epidemiological parameters had the smallest relative influence on final prevalence predictions; disease prevalence is typically over-estimated when failing to account for the complexities of a population's demography (Fig. S6, Supporting Information).

Wild pigs *Sus scrofa* might also represent an external infection source or reservoir for tuberculosis, although there is no documented case of endemic *M. bovis* infection in Australian wild pigs or boar in the absence of other infected hosts (cattle and buffalo). Corner *et al.* (1981) concluded that transmission

from live pigs to cattle or buffalo seems improbable because of the low prevalence of generalized disease, the absence of pulmonary lesions, the lack of other obvious routes of excretion from infected pigs and the low incidence of contact between the various species (Corner *et al.* 1981). There is, however, anecdotal evidence that the presence of tuberculosis in cattle and pigs is related. Two surveys done from 1973 to 1976 (Corner *et al.* 1981) and in 1992 (McInerney, Small & Caley 1995) showed that buffalo densities declined from 20 to 45 km⁻² during the first survey (pre-BTEC culling) to 0.1 km⁻² during the latter (post-BTEC) – during that same interval, the tuberculosis prevalence in pigs declined from 47.7% to 6.2% (McInerney, Small & Caley 1995). Elsewhere (e.g. Spain), wild boar *S. scrofa* can be an important reservoir of tuberculosis (and are not just dead-end hosts) (Naranjo *et al.* 2008). In New Zealand, the role of wildlife other than introduced common brushtail possums *Trichosurus vulpecula* in transmitting tuberculosis is unclear, but some introduced feral deer species (e.g. *Cervus* spp.), sheep, goats, pigs, cats *Felis catus*, ferrets *Mustela putorius* and hedgehogs *Erinaceus europaeus* might act as amplifier hosts (Coleman & Cooke 2001). In the USA, tuberculosis has re-emerged despite control in the main wildlife host, white-tailed deer *Odocoileus virginianus*, possibly due to other species such as raccoons *Procyon lotor*, opossums *Didelphis virginiana*, foxes *Vulpes vulpes* and coyotes *Canis latrans* acting as reservoirs (Witmer *et al.* 2010). The bottom line is that pigs appear to be important hosts of tuberculosis because they are widespread and increasingly in contact with livestock and other wildlife susceptible to the disease (Meng, Lindsay & Sriranganathan 2009); this argues for integrated, multispecies approaches to eradicate tuberculosis in free-ranging populations (Coleman & Cooke 2001).

Effective disease monitoring and control are becoming more challenging given increased global trade in live animals and greater demand for livestock protein arising from increasing human populations and standards of living (Schiller *et al.* 2010). New monitoring and testing technologies offer greater detection specificity and a better understanding of wildlife reservoirs for common and emerging livestock disease (Schiller *et al.* 2010), meaning that we are ideally placed to provide empirical support for effective disease control and monitoring efficiency. The development of biologically realistic yet easy-to-use software applications is a necessary component of this process. We have shown the practical and theoretical utility of just such a modelling assemblage combining epidemiological and demographic uncertainty within an individual-based context. The possibilities for further development and application of this coupled model approach are vast.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Schematic diagram of the interface between VORTEX and OUTBREAK programs as controlled by METAMODEL MANAGER.

Fig. S2. Deterministic stable-stage distribution for buffalo from a tuberculosis prevalence model run in VORTEX only.

Fig. S3. Mean progression of tuberculosis and estimated population size of free-ranging swamp buffalo.

Fig. S4. Predicted reduction in tuberculosis prevalence at various proportional culling rates.

Fig. S5. Reduction in tuberculosis infection rates in domestic and free-ranging cattle and buffalo during the Australian Brucellosis and Tuberculosis Eradication Campaign.

Fig. S6. Disease-prevalence comparison between the fully METAMODEL MANAGER-coupled VORTEX-OUTBREAK model and a demographically simplified OUTBREAK-only model.

Appendix S1. Supporting methods (software information, disease parameters for OUTBREAK, deterministic Reed-Frost model, demographic parameters for VORTEX).

Appendix S2. Example VORTEX, OUTBREAK and METAMODEL MANAGER computer code.

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