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PRIORITY CONTRIBUTION

Models predict that culling is not a feasible strategy to prevent extinction of Tasmanian devils from facial tumour disease

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Summary

1. Culling, either of all animals or infected animals only, is often suggested as a way of managing infectious diseases in wildlife populations. However, replicated experiments to investigate culling strategies are often impractical because of costs and ethical issues. Modelling therefore has an important role. Here, we describe a suite of models to investigate the culling of infected animals to control an infectious cancer in the Tasmanian devil *Sarcophilus harrisii*.

2. The Tasmanian devil is threatened by an infectious cancer, Tasmanian devil facial tumour disease. We developed deterministic susceptible, exposed and infectious (SEI) models with differing ways of incorporating the time delays inherent in the system. We used these to investigate the effectiveness for disease suppression of various strategies for the removal of infected animals.

3. The predictions of our models were consistent with empirical time series on host population dynamics and disease prevalence. This implies that they are capturing the essential dynamics of the system to a plausible extent.

4. A previous empirical study has shown that removals every 3 months did not appear to be sufficient to suppress disease in a semi-isolated infected population. Our models are in accordance with this observed result. The models further predict that while more frequent removals are more likely to be effective, the removal rate necessary to successfully eliminate disease may be too high to be achievable.

5. *Synthesis and applications.* Our results, in association with a previous experimental study, show that culling is unlikely to be a feasible strategy for managing Tasmanian devil facial tumour disease. Similar conclusions have been reached in studies of other wildlife diseases. We conclude that culling is rarely appropriate for controlling wildlife diseases and should only be attempted if models predict that it will be effective.

Key-words: culling, emerging infectious disease, latent period, mathematical modelling, Tasmanian devil, time delays, wildlife management

Introduction

Infectious disease threatens many wildlife populations (Smith, Acevedo-Whitehouse & Pedersen 2009; Thompson, Lymbery & Smith 2010), but managing disease in free-ranging populations is difficult (Wobeser 2002). Culling, whether of all individuals regardless of infection status or targeted at infected animals only, is often suggested as a management strategy (Woodroffe *et al.* 2006; Davidson *et al.* 2009; Wasserberg *et al.* 2009). Culling programmes are extremely resource intensive and may be ethically controversial. It is logistically impossible to investigate many possible alternative removal strategies experimentally. Models can identify those alternatives that have the best prospects for success. Here, we describe the development of a suite of models to investigate the use of culling of infected animals to control an epidemic of an infectious cancer in Tasmanian devils *Sarcophilus harrisii* (Boitard, 1841).

Tasmanian devil facial tumour disease (hereafter DFTD) is threatening to cause the extinction of the largest surviving marsupial carnivore. Signs typical of the disease were first detected in north-east Tasmania in 1996. DFTD has subsequently spread over the majority of the range of the Tasmanian

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devil, leading to an overall population decline of at least 60%. Where the disease has been present for 5 or more years, there have been population declines in excess of 90% (Lachish, Jones & McCallum 2007) with an almost complete disappearance of individuals older than 3 years of age (Jones *et al.* 2008). DFTD is an infectious cancer in which the tumour cells themselves are the infective agent, thought to be spread between individuals by biting (Pearse & Swift 2006; Siddle *et al.* 2007). Much biting occurs during sexual interactions (Hamede, Jones & McCallum 2008). The disease may therefore have the characteristics of a sexual transmitted disease, including frequency-dependent transmission (McCallum, Barlow & Hone 2001). High prevalence of infection is maintained and ongoing population declines continue in areas where the disease is well-established, consistent with transmission being frequency- rather than density-dependent (McCallum *et al.* 2009). This host-specific disease may therefore lead to the extinction of its host (de Castro & Bolker 2005), and developing strategies to prevent this outcome is critical.

There are four main management strategies that could be applied to manage DFTD: removing uninfected wild animals from exposure to infection; disease suppression through removal of infected animals; identification and dissemination of resistant genotypes; and development of a vaccine (McCallum & Jones 2006). The first approach is being applied, with over 150 wild-caught animals from currently non-diseased areas having been transferred to mainland Australian zoos. However, in the medium term (until the possible extinction of both the devil and DFTD in the wild), this strategy will not maintain wild populations in currently diseased areas. Research is currently in progress to determine whether resistant animals can be identified (e.g. Woods *et al.* 2007; Siddle *et al.* 2010) and to attempt to develop a vaccine (Woods *et al.* 2007), but as yet there is no clear indication that either strategy will be successful.

Disease suppression through removal of infected individuals is the only strategy that can currently be tested in the field to manage the disease in wild, infected populations. 'Test and cull' is widely used to control disease in livestock but has rarely been applied in wild animals (Wobeser 2002; but see Wasserberg *et al.* 2009; Treanor *et al.* 2011, in press). Tasmanian devils are highly trappable, DFTD is visible on external examination, and it is likely that most transmission occurs from large, friable tumours. Removal of infected individuals therefore might be expected to be effective.

The strategy has been trialled on the Forestier Peninsula, an almost completely isolated peninsula in south-east Tasmania (Jones *et al.* 2007; Lachish *et al.* 2010). The peninsula (42°03′53″S, 148°17′14″E), approximately 100 km^2 in area, is connected to the remainder of Tasmania by a narrow isthmus cut by a canal, across which there is a single bridge. Shortly after the arrival of the disease in mid-2004, the population size was estimated at approximately 120 individuals (Lachish *et al.* 2010). From June 2004 to December 2010, all individuals captured with detectable disease were removed and euthanized. Trapping within a 70-km^2 area of the peninsula, using 10-night trapping sessions with 40–50 traps, was conducted biannually in 2004 and 2005, increasing to four to five trapping sessions per year in 2006 onwards. The trial cost in excess of $200 000 Australian dollars per year, despite being on a relatively small spatial scale.

Mark–recapture analysis estimated the probability of capture within a session at between 0·57 and 0·94, depending on the trapping session. Despite this intensive effort and these high recapture rates, there is no clear evidence to date that the removals have reduced the rate of transition from healthy to diseased status in comparison with a comparable unmanipulated site at the Freycinet Peninsula (Lachish *et al.* 2010).

In this study, we modelled the effects of removal of infected individuals on the interaction between Tasmanian devils and DFTD. Our first objective was to estimate the likelihood of success in the long term of the removal programme on the Forestier Peninsula. Our second objective was to determine whether there are modifications that could be made to this programme to increase this likelihood of success.

Materials and methods

BIOLOGY AND EPIDEMIOLOGY RELEVANT TO MODEL STRUCTURE

Tasmanian devils are seasonal breeders, with most matings occurring from mid-February to mid-March. After a short gestation (14–22 days), up to four young may be suckled, which emerge from the pouch in July through August and become independent of their mother by early February (Hesterman, Jones & Schwarzenberger 2008). Devils have a relatively short life span in the wild (<6 years) and can reliably be aged in the field up to the age of 3 (Jones, Barmuta, Sinn & Beeton, unpublished data). Few females reproduce before 2 years of age, although there is evidence of a substantial minority of 1-year-old females carrying young in infected populations (Jones *et al.* 2008).

There is no clear evidence of seasonality in prevalence (McCallum *et al.* 2009). Tumours have been reported from very few individuals <1 year of age, and prevalence is substantially lower in 1- to 2-year-olds than in individuals older than 2 (McCallum *et al.* 2009). The disease appears to be invariably fatal, with very few individuals surviving more than 6 months beyond the first appearance of clinical signs. There is no evidence thus far of acquired or innate resistance to infection. The latent period of the disease is currently unknown, although there is some evidence that it may be lengthy – up to 12 months (Pyecroft *et al.* 2007).

MODEL STRUCTURE

We used a susceptible, exposed and infectious (SEI) framework, with no resistant class. In all but our initial model, we explicitly included age structure. Age structure and associated time delays are critically important in this system. Both mortality and fecundity are strongly age-dependent, as is disease transmission (see McCallum *et al.* 2009). In addition, the latent period of the disease needs to be dealt with as a distributed delay. We investigated a range of ways of incorporating time delays because the way in which they are modelled can have both qualitative and quantitative effects on model predictions.

There are many ways to incorporate age structure and time delays such as the latent period into epidemiological models. Matrix-based

models (Caswell 1989) are useful for dealing with discrete age classes; however, stability problems as a result of nonlinearity can arise when the iteration timestep used in these models is too large (Gyllenberg, Hanski & Lindstrom 1997; Henson 1998). They are often appropriate when epidemic processes are completed within a single timestep (Gerber *et al.* 2005), which is not the case for DFTD (McCallum *et al.* 2009). We therefore used models that are continuous in time, which are often more useful for dealing with time dependencies that occur on multiple scales, such as the seasonal breeding in the Tasmanian devils and the latent period in the tumour.

All models were implemented using the R programming language (version 2.10.1, R Development Core Team 2009).

SIMPLE SEI MODEL

We began with a very simple and widely used (e.g. Anderson & May 1991) ordinary differential equation (ODE) model, in which the population is separated into three classes: susceptible (S), exposed (E) and infectious (I). Following empirical evidence from McCallum *et al.* (2009), we assumed frequency-dependent transmission. The model also included logistic density dependence in host fecundity in the absence of disease. We modelled removals proportional to the size of the infected population I at a constant per capita rate per unit time ρ (see Appendix S1, Supporting information).
The coupled ODE system takes this form:

$$\frac{dS}{dt} = bN(1-N) - \mu S - f(S;I;N) \qquad \text{eqn 1}$$

$$\frac{dE}{dt} = f(S;I;N) - (k+\mu)E \qquad \text{eqn 2}$$

$$\frac{dI}{dt} = kE - (\mu+\alpha+\rho)I \qquad \text{eqn 3}$$

The total population is represented by N, where $N = S + E + I$. Here, t represents time in years, b is the birth rate per animal per year, μ is the mortality rate in the absence of disease, $k = 1/L$ models the latent period L of the disease, α is the disease-specific mortality rate, ρ represents the removal effort on infectious animals, and $f(S; I; N) = \beta SI/N$ is the frequency-dependent transmission function. The populations have been scaled by carrying capacity to make S, E, I and N dimensionless.

The model has three equilibrium scenarios that can be calculated analytically: host extinction ($S = E = I = 0$), disease eradication, ($S = N, E = 0, I = 0$) and disease–host coexistence. When varying the removal rate ρ, there are two bifurcation points that define the points of transition between equilibria. The first (ρ_1) represents the point at which the removal effort is enough to avoid host extinction but not eliminate disease, whereas the second (ρ_2) represents a removal rate sufficient to eradicate disease from the host population.

AGE-STRUCTURED ODE MODEL

To introduce age structure, we separated population classes S, E and I into age classes S_i, E_i and I_i with $i = 0$–4, representing age classes 0–1, 1–2, 2–3, 3–4 and 4+, respectively.

In our simple SEI model, the time delay associated with the latent period has a negative exponential distribution, which is unlikely to be a plausible representation of the actual distribution of latent periods. A more realistic and flexible way of modelling distributed delays (Wearing, Rohani & Keeling 2005) is to create m-1 intermediate classes between stages, each with exponential transfer. The probability distribution of transfer from one stage to the next then becomes a gamma distribution $\Gamma(m,1/m)$. As m increases, the mean remains constant at one but the variance decreases, with large m approximating a delta function $\delta(t\text{-}1)$, as is assumed by a matrix model approach. We applied this approach to both the age structure (with m-1 classes) and latent period (with n-1 classes).

As all reproduction does not occur on a single date, a distributed delay is actually a more realistic assumption than a fixed delay. We chose a value of $m = 10$, which corresponds to a variance in the 1-year age-class transition of 0·1 years. It is highly likely that the latent period is variable with a frequency distribution depending on the infective dose, the genotype of the recipient and the site of infection. The limited empirical information available (Pyecroft *et al.* 2007) includes anecdotal observations of latent periods between 3 and 12 months; $n = 4$ approximates this amount of variability.

The system of equations for this model can be found in Appendix S2 (Supporting information).

We used three different pairings of m and n in our results.

1. $m = 1$ and $n = 1$, a basic coupled ODE model with no intermediate steps between age classes or exposed classes.
2. $m = 10$ and $n = 4$, using a narrow distribution for ageing and making a best guess at the latent period distribution.
3. $m = 10$ and $n = 10$, using a narrow distribution for both the ageing and latent period distributions.

DELAY DIFFERENTIAL EQUATION MODEL

An alternative way of handling time delays is to use delay differential equations (DDEs) (Taylor & Carr 2009), which incorporate an explicit delay in both ageing and transfer between the exposed and infectious classes. These models are much more efficient than the coupled ODE model in terms of memory and computation time. A necessary simplifying assumption that ageing does not occur in the exposed and infectious classes was made. This should not make a large difference to the model results: with our parameter estimates, the time period from infection to death will be 9 months on average, so devils will age at most a year in the model structure. The system of equations for this model is contained in Appendix S3 (Supporting information).

BIFURCATION DIAGRAMS

Exact solutions for the fixed points of the age-structured equations were not possible: we therefore obtained bifurcation diagrams numerically to show the behaviour of equilibrium states with respect to changing removal effort. We modelled naive devil populations beginning at carrying capacity and with a stable age distribution, then introduced a small number of diseased animals (we arbitrarily used 1% of the population) and iterated the model over 200 years, a period sufficient for steady state to be reached.

PARAMETER ESTIMATES

We derived estimates of devil demographic parameters (shown in Table S1, Supporting information) from current knowledge of devil life history and some basic modelling (see Appendix S4, Fig. S1, Table S2 in Supporting Information). Appropriate estimates for the parameters associated with disease transmission, particularly the latent period L and the initial rate of increase in prevalence following disease introduction r_0, are harder to obtain. We also used extensive sensitivity analysis to investigate the effect of these parameters on our model predictions.

We estimated β_c, the effective contact rate between age classes for which transmission exists, from the value of $\lim_{P\to 0} \frac{1}{P}\frac{dP}{dt} = r_0$ calculated

from the model that matched a given estimate of r_0, where P is the prevalence in adult devils (over 1 year of age). The parameter r_0 here represents the initial rate of increase in the prevalence of DFTD after initial introduction.

Estimates of r_0 are available from two populations for which good prevalence data exist from the time of first disease appearance: the Freycinet Peninsula (42°03′53″S, 148°17′14″E), r_0 = 1·0055, and Fentonbury (42°38′55″S, 146°46′01″E), r_0 = 2·2644 (McCallum *et al.* 2009). Unless otherwise stated, we used the value of r_0 from Fentonbury in preference to the value from Freycinet, as at Freycinet, the localized rate of increase of disease has probably been confounded with spatial spread of the disease. The study site is a peninsula about 5 km wide and extending some 50 km from north to south, which was progressively overtaken by disease over 5 years. In contrast, the Fentonbury site is more compact, being approximately 5 × 5 km, and the measured rate of increase in prevalence is likely to be a better indication of local increase.

For most of the first year of their lives, devils live in the den (Guiler 1970). As there is no evidence of vertical transmission of the disease and infection in animals < 1 year of age is extremely rare (McCallum *et al.* 2009), we assumed that devils in the 0–1 age class are not a significant part of the infection process – hence, in our models, $\beta_{i,j}$ is defined as 0 for $i = 0$ or $j = 0$, where $\beta_{i,j}$ represents transmission from an animal of age i to one of age j. There is also evidence that the rate of transmission in 1- to 2-year-olds is lower than for older animals – for example, at Fentonbury, the transmission rate among 1- to 2-year-olds is 0·602 times that of older animals (McCallum *et al.* 2009). Thus, we set $\beta_{i,j}$ as 0·602 β_c for $i = 1$ or $j = 1$, where both i and j are positive. For other age classes, it is set to β_c. There is no evidence of any consistent sex bias in prevalence (McCallum *et al.* 2009), so sexes are treated as identical in this model.

SUPPRESSION METHODS

We investigated four potential disease suppression strategies:

1. Removing a proportion of infected devils continuously, as in the simple ODE model. This is the simplest strategy to model, but continual trapping is difficult in practice.

2. Removing a proportion of infected devils discretely every 3 months. This was the approach implemented in the Forestier Peninsula trial.

3. Removing a proportion of infected devils discretely every month. An increase in the frequency of trapping trips is a potential modification to the existing strategy.

4. Removing a proportion of infected devils continuously, while adding the same number of healthy devils. This last strategy is unlikely to be feasible but is included to separate the effects of removal of diseased devils from the effect of reducing population size by culling.

FIT TO OBSERVED TIME-SERIES DATA

We used population and disease data (Lachish, Jones & McCallum 2007; Lachish *et al.* 2010) to assess our model predictions in comparison with real data. First, we fitted the model to data from the control population on the Freycinet Peninsula site, where no removals were undertaken. The goodness-of-fit function was defined as the sum of squares of the difference in the model data from the population data at each point in time where the population data were collected, weighted inversely by the appropriate confidence interval for the population data. The model was fitted using two parameters: the carrying capacity (as the model is dimensionless) and the initial value of disease prevalence at the time when the disease was first found in the population. All other parameters were as defined earlier. It should be noted that the devil demographic parameters and r_0 were obtained from this same population over the same time period, although in a separate analysis (McCallum *et al.* 2009). In each run of the model, the simulated population represented a healthy stable age distribution until the time of disease outbreak, at which point a proportion of the population equal to the set disease prevalence was transferred to the infected class.

We then fitted the model to data from the removal trial at the Forestier Peninsula (Lachish *et al.* 2010). In this case, we fitted four parameters; the two used above, with the additional parameters of continuous removal effort and r_0, which is likely to differ between Forestier and Freycinet. In addition, we calculated the goodness-of-fit function for the model's prevalence output in an identical fashion to the above population estimate fitting. The overall goodness-of-fit function for the model is the sum of the two functions – the model is thus fitted to both the population and prevalence data with approximately equal weighting (the population size is scaled to between 0 and 1, as is prevalence). In this case, the model began with the initial conditions of a diseased population with prevalence set by the fitting parameter. At the time known to be the beginning of disease suppression, the value of ρ in our model is changed from zero to our fitting parameter value. This ad hoc model fitting procedure was intended to determine whether our model was qualitatively in agreement with the observed pattern, in contrast with more formal approaches such as approximate Bayesian computation (Toni *et al.* 2009) or trajectory matching (Cooch *et al.* 2010), which would require more data than we had available.

Results

BIFURCATION DIAGRAMS

Figure 1 shows a bifurcation diagram of the stability behaviour of equilibrium states of the basic SEI model with respect to the removal rate ρ. If the population becomes disease-free at equilibrium, then increasing the removal rate further than necessary can cause a transition into extinction, but this situation does not occur here for any biologically realistic parameter estimates.

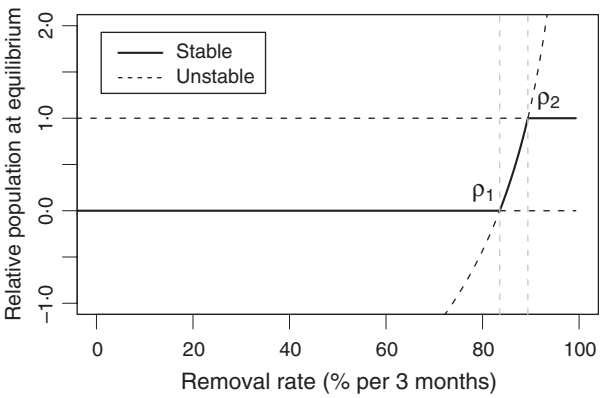

Fig. 1. Bifurcation diagram for basic susceptible, exposed and infectious model. The two vertical dotted lines represent the transition points ρ_1 and ρ_2. Parameter values from Table S1 (Supporting information).

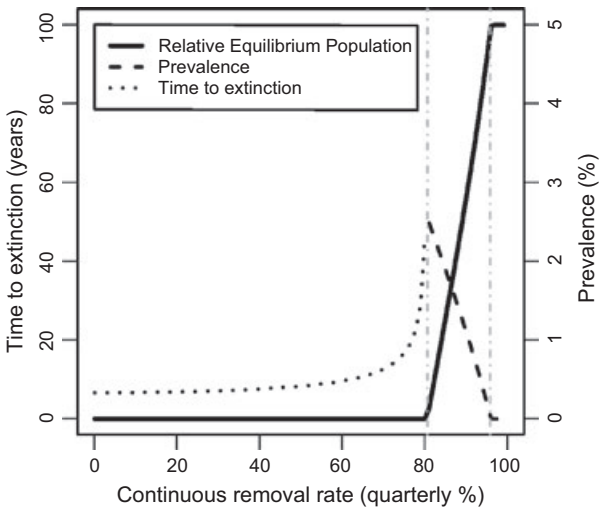

Fig. 2. Plot of relative equilibrium population, equilibrium disease prevalence and time to extinction against removal rate for the coupled ODE method with $m = 10, n = 4$ and for Strategy 1. Parameter values from Table S1 (Supporting information). State changes occur at $\rho_1 = 80{\cdot}67\%$ and $\rho_2 = 95{\cdot}86\%$ as indicated by the grey dotted vertical lines.

Figure 2 shows a bifurcation diagram obtained numerically from the age-structured ODE model with gamma-distributed delays. The prevalence is the proportion of infected adults in the stable state after 200 years (we did not observe any periodic or quasi-periodic outcomes for our parameter values). The time to extinction (TTE) is the amount of time required for the population to reach 1% of the carrying capacity, provided this event occurs within 200 years. In all our numerical results, ρ_1 and ρ_2 represent the points at which 1% and 99% of the population persist, respectively, instead of 0% and 100% as in the analytical case.

Without removals, all model variants predicted extinction of the devil population within 10 years. With continuous removal, there was no marked increase in the expected time until extinction until removal rates were close to ρ_1 (Fig. 2). However, Fig. 2 further shows that between the two transition points, prevalence is low (< 3%), declining to zero at ρ_2. Devil populations can thus only coexist with the disease in the long term for low levels of prevalence. As most of the dynamical information can be summarized by giving the parameters ρ_1 and ρ_2, Table 1 provides a comparison of these parameters for the different removal strategies.

Table 1. Transition point values for varying modelling methods and strategies. ρ_1 represents the minimum removal rate that avoids host extinction but does not eliminate disease in the model; ρ_2 represents the minimum removal rate that eradicates disease from the host population. The table contains '–' if no removal rate will achieve the goal for the given combination of model and strategy. To enable comparisons, the transition points are expressed in terms of percentage of animals removed per quarter, even where the removal rate is continuous or monthly. Parameter values from Table S1 (Supporting information)

	Simple SEI model		Coupled ODE model						DDE model	
			$m = 1$, $n = 1$		$m = 10$, $n = 4$		$m = 10$, $n = 10$			
Strategy	ρ_1	ρ_2	ρ_1	ρ_2	ρ_1	ρ_2	ρ_1	ρ_2	ρ_1	ρ_2
1 (continuous removal)	84·18	89·85	62·82	89·21	79·03	96·21	83·77	97·47	92·08	98·02
2 (monthly removal)	84·51	90·72	61·94	90·01	78·94	97·49	84·16	98·61	–	–
3 (quarterly removal)	–	–	69·81	–	94·31	–	–	–	–	–
4 (quarterly removal of infected with replacement)	80·74	–	49·48	–	64·65	–	70·42	–	–	–

DDE, delay differential equation; ODE, ordinary differential equation; SEI, susceptible, exposed and infectious.

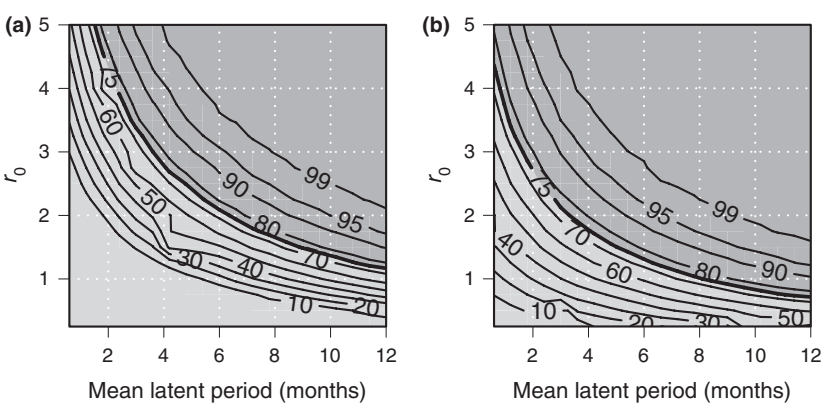

Fig. 3. Sensitivity analysis for varying latent period L and disease parameter r_0 holding all other parameters constant at the default values with ρ_1 (Fig. 3a) and ρ_2 (Fig. 3b) as the response variables. The $m = 10$, $n = 4$ model is used here with a continuous removal strategy. The black line at 75% is an estimate of the maximum removal effort possible, taking into account the existence of a cryptic population.

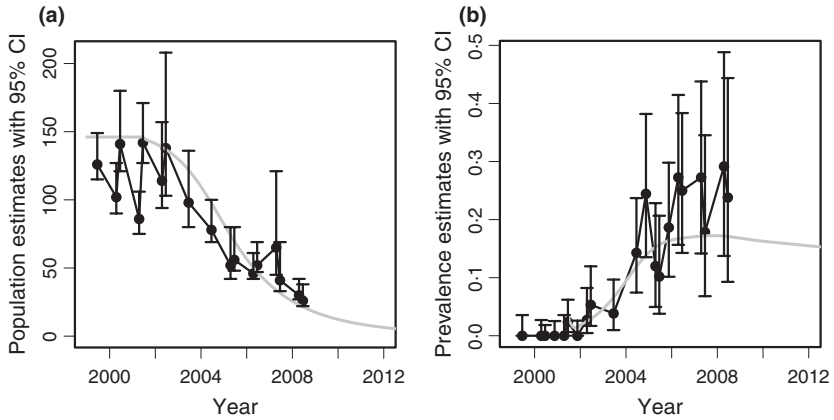

Fig. 4. Comparison of model to Freycinet data. The black line represents the actual estimate of the population (Fig. 4a) and prevalence (Fig. 4b) in the Freycinet Peninsula from trapping surveys, with 95% confidence intervals. The grey line represents the best-fit model estimate of disease progression. The $m = 10$, $n = 4$ model is used here with a continuous removal strategy.

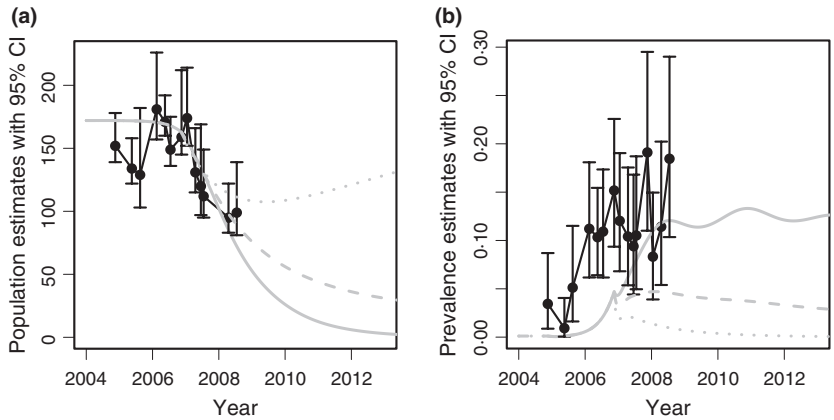

Fig. 5. Modelling potential disease suppression scenarios. The black line represents the actual estimate of the population (Fig. 5a) and prevalence (Fig. 5b) in the Forestier Peninsula from trapping surveys, with 95% confidence intervals. The solid grey line represents the best-fit model, whereas the dashed line represents increasing removal effort in this model above ρ_1 (90%) and the dotted line above ρ_2 (99%). The $m = 10$, $n = 4$ model is used here with a continuous removal strategy.

SENSITIVITY ANALYSIS

Of the models presented, the most representative of the actual population is probably the coupled ODE model with $m = 10$ and $n = 4$. For this model, Fig. 3 shows contours of the removal rates necessary for disease elimination (ρ_1) and prevention of host extinction (ρ_2) as a function of the latent period and the rate of increase per year in prevalence following first disease introduction r_0.

DATA FITTING

For the Freycinet Peninsula, we found a best-fit carrying capacity value of 121 and an initial prevalence value of 1·27%, which corresponds to about two adults being initially infected. The model results (see Fig. 4) for the most part lie within the confidence intervals of the real population estimates, although the model fit appears to overestimate the population in or around 2005. For the suppression trial at the Forestier Peninsula, we found a best-fit carrying capacity value of 172, an initial prevalence value of 0·09%, an r_0 value of 2·5092 and a quarterly continuous removal effort of 69·0%. Although the fit is not highly sensitive to the latter parameter, this value corresponds with what we would expect from the field trapping effort. The best-fit value for r_0 is slightly higher than that found at Fentonbury (2·2644; McCallum *et al.* 2009) but well within the estimated 95% confidence interval.

The results (see Fig. 5) again appear to compare well in the case of the population estimate, with the model results only lying outside the confidence intervals of the real population estimates at one point in the time series. However, the model generally underestimated prevalence. The two additional scenarios involving an increased removal effort demonstrate the time-scale in which we are likely to see results if disease suppression is successful or is made successful. In each case, only a few years are required to tell what the likely long-term outcome is likely to be – in the 90% case, disease coexistence with its host, and in the 99% case, total disease eradication.

Discussion

Empirical analysis suggests that an attempt to manage DFTD by removal of infected individuals on the Forestier Peninsula has not, after 2·5 years, resulted in a decline in prevalence or population recovery (Lachish *et al.* 2010). A primary objective of this modelling exercise was to investigate whether higher removal rates or different removal strategies might have been successful. Given the results in Table 1, it appears that a very high removal rate would be required to remove disease or even to prevent host extinction. The strategy of removing individuals on 3-monthly field trips used in the removal trial is unlikely to be effective. If removal occurs on a continuous basis, prospects for managing the disease are improved, simply because

the mean time for which an infected animal remains in the population before removal is reduced. However, continuous removal is difficult logistically, requiring trapping teams to be working continuously. It is also likely to result in trap fatigue and lowered capture rates.

In excess of 20% of the devil population at the Forestier trial removal site is never caught in traps, based on recent DNA analysis of scats and hair samples (M.E. Jones, personal communication). The maximum possible removal rate of infected devils is thus $< 80\%$. Given our results, this obviously presents a pessimistic picture of the potential success of disease suppression. Finding ways to deal with trap-shy animals is vital.

The conclusion that a very high removal rate is needed is independent of the details of the model, although Table 1 shows that incorporation of realistic delay distribution increases the removal rate necessary.

Our results emphasize the influence of time delays and the way in which they are modelled. The results for the coupled ODE model with $m = 10$ and $n = 10$ are substantially different to those for the DDE model. This could be due to the assumption made in the DDE model that animals do not age once they are exposed to the disease, or to the difference between the distributions of ageing and latent period between the models. A much higher value for m in the coupled ODE model would more closely approximate the DDE model, shedding light on the impact of these structural differences. Nevertheless, the gamma-distributed delay approach of Wearing, Rohani & Keeling (2005) provides a powerful means of realistically including distributed delays.

From the sensitivity analysis, it is evident that the longer the latent period, the more difficult it is to eliminate disease or prevent host extinction. This is not surprising, because for a given rate of increase in prevalence r_0, the basic reproductive number R_0 increases with latent period (McCallum *et al.* 2009). Unfortunately, there is still little more than anecdotal information available on the frequency distribution of the latent period for DFTD. For the rates of increase in prevalence observed in the field, which are in the range of 1–2·25 year^{-1}(McCallum *et al.* 2009), it is clear from Fig. 3 that a removal strategy is unlikely to be successful if the mean latent period is in excess of about 6 months. On the other hand, if the mean latent period is 3 months or less, the prospect of successful disease suppression is much greater.

The model fitting in Fig. 4 suggests that the model is capable of capturing the main trends in both population size and prevalence on the Freycinet Peninsula. The prevalence is not as well modelled for the Forestier Peninsula as was the case of Freycinet: the model fails to capture the initial rapid increase in prevalence, despite the fitted value of r_0 being in excess of the value estimated for either the Freycinet or Fentonbury populations. This may be because the model is assuming a continuous removal, whereas in reality removal occurs at 3-monthly intervals.

Coexistence of Tasmanian devils and the tumour was possible for only a very small range of removal rates. This is a consequence of frequency-dependent transmission and means that in this particular case, a stochastic model would provide limited additional information. Either the removal rate is sufficient for control of infection or it is not, and issues such as stochastic extinction of the host at low density or fadeout of the pathogen at low prevalence are unlikely to be important.

Heterogeneity in the structure of the host population and in contact rates is potentially more important. We have assumed that all devils are equally susceptible to disease. Selective removal of infected animals (which by definition would have susceptible genotypes) might have the additional benefit of increasing the probability that resistant animals would breed with each other. However, recent analysis of MHC types in Tasmanian devils shows that the majority of devils in the Forestier area have MHC types indistinguishable from the tumour and that this area has particularly low MHC diversity in comparison with devil populations in the rest of Tasmania (Siddle *et al.* 2010). We have also omitted the observed increased breeding by 1- to 2-year-old females in populations affected by DFTD (Jones *et al.* 2008; Lachish, McCallum & Jones 2009). Continuing population decline in diseased populations (Lachish, Jones & McCallum 2007; Lachish, McCallum & Jones 2009) shows that this increased breeding is not sufficient to compensate for the effects of disease.

We have modelled transmission using a mean field assumption. Contact networks in Tasmanian devils are significantly different from randomly connected networks (Hamede *et al.* 2009), but they do not have a high degree of aggregation (which would facilitate transmission relative to a random network); nor do they have high levels of transitivity (which would inhibit transmission relative to a random network). It is therefore unlikely that culling would produce major changes in the structure of the devil contact networks.

Conclusion

Our modelling shows that managing DFTD through selective culling is difficult, despite high trappability and the ability to diagnose infection by inspection on capture. As transmission is frequency-dependent, disease progresses rapidly and is likely to lead to host extinction within 1–2 decades without intervention. Nevertheless, the models show that density-dependent transmission is not a precondition for selective culling to be a feasible control strategy for wildlife populations: a sufficiently high removal rate of diseased animals is capable of eliminating or suppressing disease. A diagnostic test capable of detecting disease before exposed individuals become infectious would substantially reduce the removal rate necessary.

Several other studies, based on both empirical and modelling approaches, have found that culling is rarely viable as a strategy for controlling wildlife disease. Hallam & McCracken (2011) found that culling did not control white nose syndrome in bats for any of the scenarios they explored through simulation modelling. Localized culling of badger populations in the UK to control bovine tuberculosis infection appears sometimes to actually increase disease prevalence by disrupting badger social structure (Donnelly *et al.* 2003, 2006; Woodroffe *et al.* 2006). Using a spatially specific stochastic model, Davidson *et al.* (2009) suggested that very high culling levels and

multiple culls were required to control paratuberculosis in rabbits. Wasserberg *et al*. (2009) modelled managing chronic wasting disease in deer by selective culling, assuming both density-dependent and frequency-dependent transmission. Culling was much more effective when transmission was density-dependent. Theoretically, unselective culling can actually increase disease prevalence if transmission is frequency-dependent (Choisy & Rohani 2006). This outcome relies on the pathogen being strongly immunizing and on the presence of density-dependent regulation of the host population. Culling can then increase the proportion of susceptible individuals in the population. We recommend that culling should only be attempted once appropriate models have shown that it is likely to be effective.

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Supporting Information

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

Fig. S1. Life expectancy versus required removal rates.

Table S1. Parameter estimates used for models.

Table S2. Proportion of 3 + year olds vs. life expectancy.

Appendix S1. Analysis of the ODE system.

Appendix S2. Description of the age-structured SEI system.

Appendix S3. Analysis of the DDE system.

Appendix S4. Discussion of life expectancy.

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