CHAPTER ELEVEN

Emergence, transmission and evolution of an uncommon enemy: Tasmanian devil facial tumour disease

MENNA E. JONES, RODRIGO HAMEDE, ANDREW STORFER, PAUL HOHENLOHE, ELIZABETH P. MURCHISON AND HAMISH MCCALLUM

11.1 Introduction

Twenty years ago, the Tasmanian devil (*Sarcophilus harrisii*) was a common species. The largest extant marsupial predator (Jones, 2003), Tasmanian devils achieved notoriety locally as an 'odious scavenger' and internationally as a comical and belligerent cartoon character. In 1996, a wildlife photographer took images of a Tasmanian devil in north-east Tasmania with large tumours on its head (Hawkins et al., 2006; Figure 11.1). By 2009, the species was listed as Endangered (Hawkins et al., 2009). By 2017 the tumour disease had spread to most of the Tasmanian devil's geographic range in the island state of Tasmania (www.tassiedevil.com.au/tasdevil.nsf) (Figure 11.2), causing >90% local population decline (Lachish et al., 2007; Lazenby et al., 2018). Concern has been raised for both the extinction of the Tasmanian devil and also further extinctions that might arise as the loss of this apex predator triggers trophic cascades through Tasmanian food webs (McCallum & Jones, 2006; Jones et al., 2007; Hollings et al., 2016). As the apex predator in Tasmania (following the extinction of the larger thylacine, *Thylacinus cynocephalus*), the Tasmanian devil likely plays a useful ecological role in suppressing feral cats and thereby protecting the biodiversity of smaller vertebrate prey species (Hollings et al., 2016).

This chapter reviews Tasmanian devil facial tumour disease (DFTD), now a classic case study, to show how theory and data can be combined to manage an emerging and evolving conservation threat from a novel and unusual disease. Emerging infectious diseases (EIDs) are an increasing global threat for biodiversity, and host naivety to these novel pathogens often leads to high susceptibility and severe population impacts (Daszak et al., 2000; Tompkins et al., 2015). For most EIDs, we have poor knowledge of the ecology of the pathogen and are unable to assess the extent of conservation threat (McCallum & Jones, 2006). We describe the emergence, unfolding epidemic, and now the

Paul Hohenlohe, Department of Biological Sciences, University of Idaho, Moscow, ID, USA

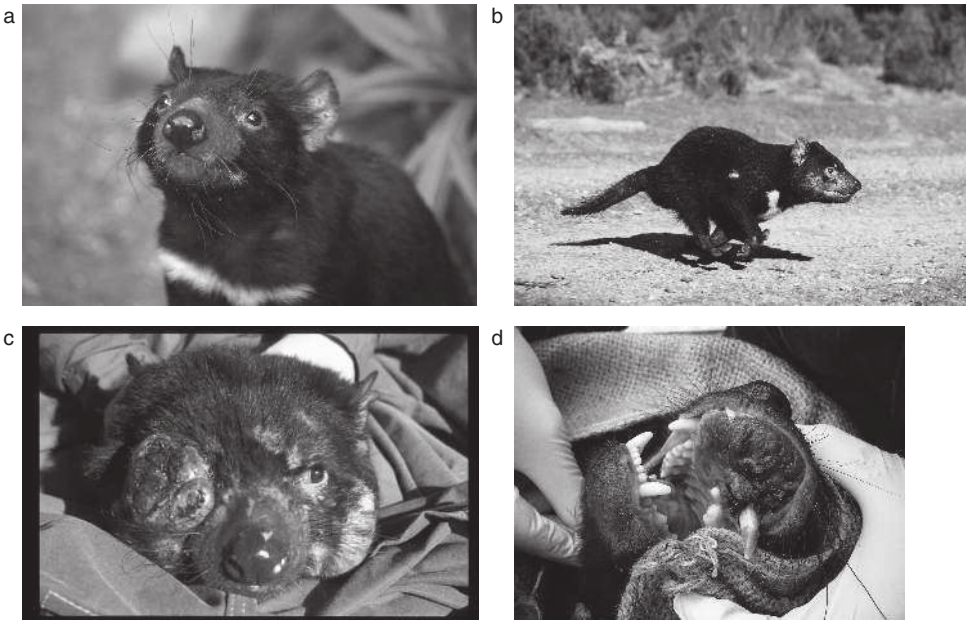

Figure 11.1 Images of (A,B) a healthy Tasmanian devil, and (C,D) of facial tumours. Photo credits: Menna Jones (A,C), Sarah Peck (B), Rodrigo Hamede (D). (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

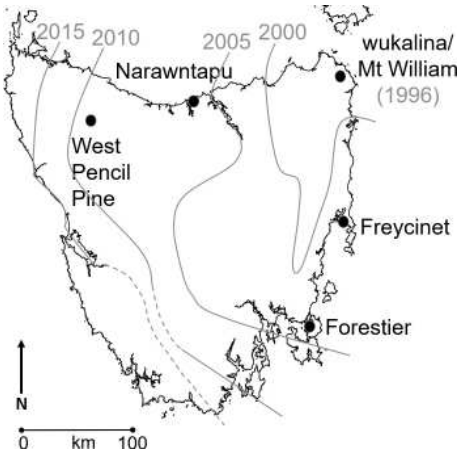

Figure 11.2 Map of Tasmania showing the timing of the spatial spread of DFTD and key research sites.

rapid evolutionary response to a transmissible cancer, a rare and different type of natural enemy (*sensu* Lafferty & Kuris, 2002) in which the infectious agent is a live cancer cell (Box 11.1). Our first step was to develop a decision tree to guide research and management of this novel transmissible cancer (McCallum &

Jones, 2006). We then quantified transmission in wild populations to identify control options and predict the epidemic outcome. Our current focus is quantifying rapid evolution in host and pathogen to understand how adaptation in the devil and potentially host–pathogen coevolution might influence transmission and epidemic outcome, and to understand how management actions can facilitate beneficial rather than detrimental adaptation. The Tasmanian devil–DFTD host–pathogen system provides a rare opportunity to study a wildlife disease in all stages of existence across the entire geographic range of a natural host species (from pre-emergence to emergence, to post-emergence decline, and potentially even endemism and host recovery).

11.2 Prioritising conservation actions and research for an emerging disease

By the time it was established that DFTD posed a conservation threat, it was too late to stamp out the disease through a culling approach. Sporadic detections of DFTD between 1996 and 2001 (Hawkins et al., 2006), and reaction-diffusion modelling (Beeton, 2011), suggest that the index case occurred somewhere in the north-east of Tasmania, probably in the early 1990s as there are no prior records of a similar disease (Pyecroft et al., 2007). In 2001–2002, the disease entered and spread 10 km along the Freycinet Peninsula, a long-term study site on the East Coast of Tasmania (Figure 11.2), causing significant localised population decline. This triggered a snap-shot trapping survey in 2003 which revealed unexpectedly low numbers of devils across the north-eastern quarter of Tasmania (Mooney, 2004).

The first detection of the disease was in 1996 at wukalina/Mt William National Park in the far north-east of Tasmania (Figure 11.2). DFTD has spread steadily westwards and southwards, currently covering most of the island-wide distribution of the devil and predicted to reach the north-west coast within a few years. A long-term study commenced on the Freycinet Peninsula in 1999, two years prior to local disease outbreak in 2001. The Forestier Peninsula was the site of a culling trial, commencing with disease outbreak in 2004. A second long-term study site was established at West Pencil Pine in 2006. Research and genetic samples collection was established in 1999 at Narawntapu.

How should you proceed when an emerging disease presents a serious conservation threat but you have little information? DFTD was used as a case study to develop a decision tree to address this wider issue of prioritising management and research for emerging diseases (Figure 11.3; McCallum & Jones, 2006). Needing to take action in the face of uncertainty is common to many ecological problems (Burgman, 2005). Delaying action until better information is available can result in greater costs and even foreclosure on the option of control, particularly when dealing with emerging diseases (Sakai et al., 2001).

Box 11.1: The nature of transmissible cancers and Tasmanian devil facial tumour disease

There are just eight known cases of transmissible cancers in nature: in dogs, in several species of marine bivalve molluscs (Metzger et al., 2015, 2016), and two in Tasmanian devils. The canine transmissible venereal tumour (CTVT) evolved ~11,000 years ago and is an evolutionarily stable cell line (Murgia et al., 2006; Murchison, 2008). Tasmanian devil facial tumour disease emerged about 20 years ago (discovered in 1996; Hawkins et al., 2006) and a second transmissible cancer (DFT2) emerged as a distinct evolutionary event more recently (Pye et al., 2016b).

Transmissible cancers are an uncommon type of natural enemy (*sensu* Lafferty & Kuris, 2002). They have some of the characteristics of a macroparasite (they grow as a macro-organism deriving nutrients from their host), but have a reproductive rate (defined by rates of cancer cell division) more typical of a microparasite. Cancers usually arise and die with their host. This is the case even for cancers associated with infectious agents: in such cancers the infectious agent such as a virus increases the probability that a host cell becomes cancerous; thus, although the virus might survive and transmit beyond its host the cancer itself will not (McCallum & Jones, 2012). In transmissible cancers, live tumour cells are the infectious agents. Transmissible cancers have taken the unusual evolutionary step to metastasise outside their host to become immortal cell lines. As tumour cells are 'rogue' host somatic cells, they do not live long outside the body of the animal. The evolution and transmission of transmissible cancers thus requires intimate and injurious contact between live tumour cells on the infected host and a break in the epidermis or mucosa of the susceptible host.

A second condition for their emergence is a mechanism for host immune system evasion. Both CTVT and DFTD downregulate expression of the Major Histocompatibility Complex (MHC) molecules which enable immune recognition of cancer cells (Siddle et al., 2013). The intimate injurious contact required for transmission of DFTD is most common in the mating season (Hamede et al., 2008), and CTVT is a venereal cancer with lesions on the genitals (Murchison, 2008). Both of these cancers would have strongly frequency-dependent transmission, as mating occurs irrespective of population density, bringing infected and susceptible individuals together.

The aetiology of the disease was not initially known. However, aetiological agent identification is not essential for more urgent conservation actions; it thus occurs relatively late in the decision tree (Figure 11.3). Indeed, transmissibility of the devil cancer was not confirmed until five years after disease

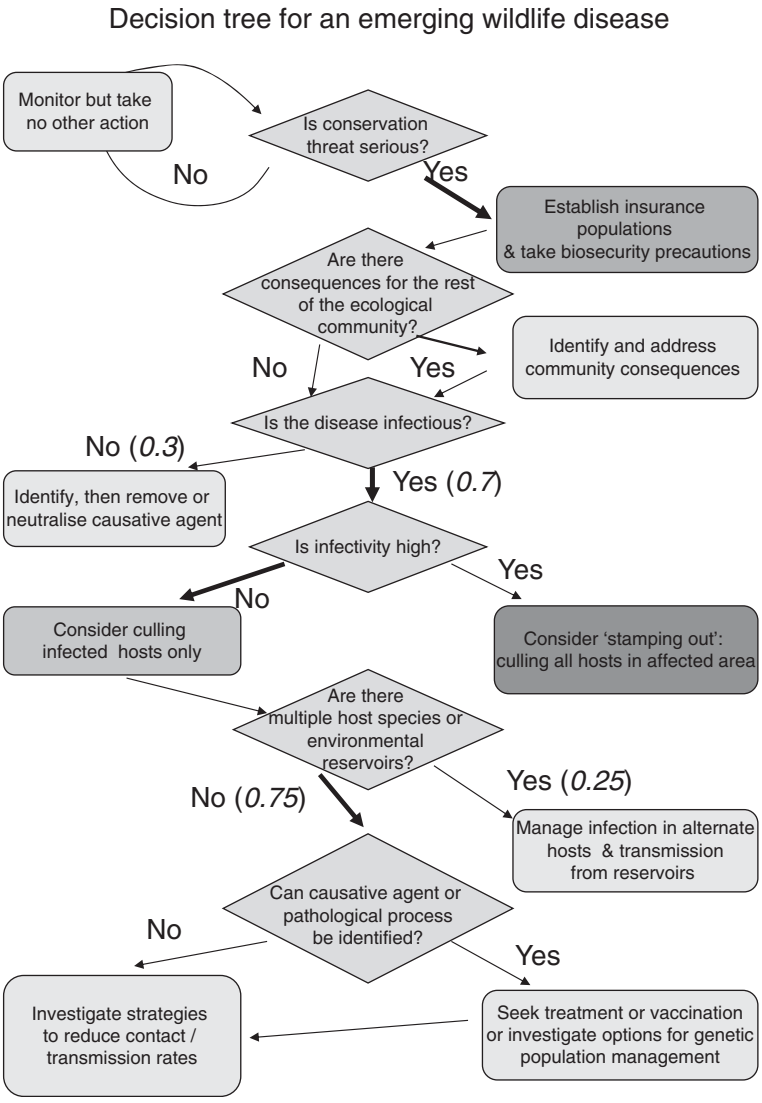

Figure 11.3 A decision tree for the management of emerging wildlife disease, with particular reference to Tasmanian devil facial tumour disease. The relative thickness of arrows indicates the current likelihood of the given path representing the true situation. Probabilities determined by consensus of expert opinion at a technical workshop on DFTD (AusVet, 2005) are shown on the arrows in italics. Colours represent the cost associated with the specified action, if it proves to be as a result of an incorrect decision: red = high, yellow/orange = medium, green = low. Reproduced from McCallum & Jones, *PLoS Biology*, 2006. (A black and white version of this figure will appear in some formats. For the colour version, please refer to the plate section.)

emergence was recognised in 2001 (Pearse & Swift, 2006). The first management actions taken by the Tasmanian government Save the Tasmanian Devil Program (STDP) were to establish an insurance metapopulation isolated from the disease (Jones et al., 2007) and apply biosecurity protocols to limit the risk of disease spread during the handling of wild devils and their transfer into captive populations (www.tassiedevil.com.au/tasdevil.nsf). The insurance metapopulation was designed to capture and retain the standing genetic diversity in devils, through the intake of founders from the wild (Jones et al., 2007; Huxtable et al., 2015). Founders included independent juveniles from then disease-free western Tasmania and orphaned pouch young from the diseased eastern populations. From 2004 to 2015, insurance populations were expanded to include intensive and free-range captive enclosures and free-living populations on an island and a fenced peninsula (Huxtable et al., 2015). Generally, larger and more natural holding facilities reduce the likelihood of genetic adaptation to captivity (Frankham, 2008), with the animals held in such facilities more suitable for wild release (Jones et al., 2007; McCallum & Jones, 2010). However, one study found that captive-management style did not influence survival, body mass change, or diet of devils one year after release (Rogers et al., 2016).

The potential for trophic cascades (Jones et al., 2007) following the decline and probable functional extinction (Hollings et al., 2015) of the Tasmanian devil over much of its range was raised as a concern right from the start of the investigation (McCallum & Jones, 2006). The extinction of the devil might be a tragedy, but the loss of the apex predator from Tasmanian ecosystems could trigger further extinctions in smaller biodiversity. This concern has been realised (Hollings et al., 2014, 2016) and will be discussed in Section 11.6.

Once urgent conservation actions have been taken to prevent extinction, early decisions that could immediately influence management of the epidemic outcome are to establish whether the disease is infectious and whether infectivity is high (Figure 11.3). Conducting experiments to establish Koch's postulates (see McCallum, 2005) would cost too much time. Instead, that the disease was infectious was established with a high level of certainty through expert opinion consensus (AusVet, 2005). This decision took into account the likely nature of the disease (possible transmissible cancer) and documented geographic spread (AusVet, 2005).

Crucially, allowing highly infectious diseases to establish may have extreme consequences including foreclosure of future control. If the basic reproductive rate R_0 is high, and the epizootic is in its very early stages, it is worth considering the feasibility of an immediate effort to 'stamp out' the disease. Stamping out, by removing all potentially infected cases, is a standard approach used with highly infectious diseases in livestock, such as foot-and-mouth disease (Scudamore & Harris, 2002). It is even possible

with human diseases, by using contact tracing to find and treat or quarantine all cases, such as occurred with SARS (Donnelly et al., 2003). Stamping out is logistically much more difficult with wild animals, and has ethical considerations for endangered species. In the case of DFTD, which spread through a wild population living in a variably dense and rugged landscape, the threat was recognised far too late to use this option.

One further decision point that needs to be addressed early is whether there are multiple host species or environmental reservoirs. If this is the case, then infection in these sources needs to be managed for infection control in the focal host to be effective. Transmissible cancers such as DFTD are likely to be restricted to the species of origin, or at the least very closely related species. DFTD is known only in Tasmanian devils, although the other naturally occurring transmissible cancer in vertebrates, CTVT, that affects dogs (Murgia et al., 2006; Murchison, 2008) can infect other canids under experimental settings (Murchison, 2008), probably because of the close phylogenetic relatedness within the Family Canidae (Wayne et al., 1997).

Based on the above reasoning, most of the research on DFTD lies at the bottom of the decision tree, including strategies to reduce transmission rates in wild populations, a potential vaccine and treatment, and genetic management (Figure 11.3).

11.3 Quantifying transmission to identify control options

In established infections, disease control rests on manipulating the transmission rate. Control options for DFTD that reduce transmission rates include chemical or immune therapies, culling, and reducing contacts between infected and susceptible individuals (McCallum & Jones, 2006). Treatment with a range of standard cytotoxic drugs, and surgical excision, were found to be ineffective against DFTD (Phalen et al., 2013, 2015), even though these are effective against CTVT (Nak et al., 2005). However, some success has been met with a potential immunotherapy treatment that uses cytokines to activate MHC upregulation on the tumour cell surface, potentially revealing the tumour to the immune system of the devil (Brown et al., 2016). Without this treatment, DFTD essentially remains hidden to the devil immune system due to downregulation of its MHC expression (Siddle et al., 2013) (Box 11.1). Another possible treatment involves immunisation with killed tumour cells, which can induce humoral and cytotoxic immune responses against DFTD cells (Kreiss et al., 2015). This response combined with the clonal nature of DFTD lends hope that developing a vaccine may be possible (Woods et al., 2015).

Two other approaches for disrupting transmission were investigated in the DFTD epidemic: selective culling of infected individuals (mid-way in the decision tree; Figure 11.3) and elucidating contact networks to identify superspreaders that could be targeted for removal. Selective culling is a more acceptable option for an

endangered species than wholesale culling (stamping out). Selective culling can be effective, particularly if the population is relatively closed, if transmission is not high, and infected individuals can be identified before they become highly infectious. The removal of infected devils was trialled on the Forestier Peninsula in south-east Tasmania (Figure 11.2; Lachish et al., 2010). Favourable conditions for culling at this site include: very little movement of devils between the peninsula and the Tasmanian mainland on a road bridge across a canal; commencement of the culling almost from the outbreak of DFTD (Lachish et al., 2010); and a relatively high and uniform recapture probability for devils of about 80% (Lachish et al., 2007). Four years of trap-and-removal, during 10-day efforts every 3 months over the entire 160 km^2 area, during which nearly 200 diseased devils were removed from the population, neither reduced the force of infection nor reduced population-level impacts relative to an unmanaged but otherwise comparable devil population on Freycinet Peninsula (Lachish et al., 2010). Population models of the culling and control sites indicated that mortality from culling appeared to simply replace mortality from disease. Deterministic susceptible–exposed–infected (SEI) time-delayed models of this system indicated that unfeasibly high levels of removal would be necessary to be effective, with almost continual trapping at very high effort required. Selective culling is probably not a feasible control option for this particular disease (Beeton & McCallum, 2011). The chance of success might be improved if a pre-clinical diagnostic test were available that enabled removal of infected individuals prior to their becoming infectious. Devils are unlikely to be infectious prior to the appearance of tumours and so a blood test to detect tumour metabolites or DNA is needed. Some progress has been made towards this goal (Tovar et al., 2011; Karu et al., 2016).

Social structure and contact networks have profound influence on disease transmission (Altizer et al., 2003). Transmission rarely occurs evenly among individuals within a population. Frequently, a small number of individuals, termed 'superspreaders', will account for a disproportionately high amount of transmission (Galvani & May, 2005; Lloyd-Smith et al., 2005). If superspreaders can be identified in wild populations, they could be targeted for culling. Devils and DFTD were among the first wildlife disease systems for which host contact networks were elucidated using the then new technology, proximity-sensing loggers on radio-collars (Hamede et al., 2009). Unlike the highly aggregated social networks for many human diseases, all devils in the population appear to be well connected. Some individuals were better connected across the population than others, but the pairs of interacting devils changed between mating and non-mating seasons. Particular male–female pairs were identified in the mating season, and specific female–female associations outside the mating season. These results suggest that there is limited potential to control DFTD by targeting specific age, size or sex classes (Hamede et al., 2009).

From this point, disease investigations moved beyond the decision tree which had guided the early and critical stages of response to this emerging and devastating disease. The next phase was to gain a better understanding of transmission (Section 11.4), and how this is influenced by evolution in the devil and the tumour (Section 11.5), to predict the epidemic outcome.

11.4 Quantifying transmission to predict the epidemic outcome

Understanding the transmission dynamics of infectious diseases is crucial for predicting spread within host populations and the eventual outcome of epidemics (Anderson & May, 1979; May & Anderson, 1979). Diseases in which transmission depends more on the frequency of contacts, rather than the density of individuals, are more likely to cause extinction because they lack a host population threshold for persistence (De Castro & Bolker, 2005). Frequency-dependent transmission is more typical of diseases where transmission occurs during breeding activity or sexual contact and infection depends on the proportion of infected individuals in populations (De Castro & Bolker, 2005).

A genuine risk of extinction of the Tasmanian devil from the facial epidemic was predicted by both a deterministic mean-field model and a stochastic individually based model based on contact networks (Hamede et al., 2009), the latter predicting faster extinction and higher extinction probabilities (McCallum et al., 2009; Hamede et al., 2012). A simple age-structured deterministic model showed that transmission of DFTD is not proportional to the density of infected hosts, which suggests a strong element of frequency-dependence in the transmission dynamics (McCallum et al., 2009). This conclusion is strengthened by transmission being dependent on injurious contact when Tasmanian devils bite each other (Box 11.1), a concentration of biting injuries in the mating season (Hamede et al., 2008), and a high force of infection sustained even when population densities reach very low levels (McCallum et al., 2009).

Despite predictions of extinction from simple deterministic models (McCallum et al., 2009), devils persist at the two longest infected field sites, Freycinet and wukalina/Mt William (Figure 11.2). This was surprising given >90% population declines and infection prevalences of 50% being sustained for at least five years at both sites. A limitation of these models is that they were developed within the SEI framework, which considers all infected individuals to be equivalent, both in terms of the disease-induced death rate and their ability to transmit infection to susceptible hosts. However, evidence suggests that both the death rate from DFTD and transmissibility depend on the size of the tumours carried by an individual host (Wells et al., 2017). Integral projection models, in which demographic parameters depend on some continuous trait of the organisms in the population (Easterling et al., 2000; Coulson, 2012) are therefore a potential improvement on the standard SEI approach for modelling DFTD dynamics.

The potential for using such models for host–parasite dynamics has recently been recognised (Metcalf et al., 2016; Wilber et al., 2016). To apply these models, it is necessary to estimate the growth function of infection on hosts that survive, and also to estimate survival, fecundity, and transmission rate as functions of disease burden. State–space models were used to estimate the first three of these functions from a 10-year time series of devil and DFTD data from West Pencil Pine (Wells et al., 2017).

This analysis produced the rather startling result that devils which become infected with tumours have otherwise higher fitness, both in terms of increased survival and increased fecundity, than devils that do not become infected (Figure 11.4A,B). The most likely explanation for this result is that transmission probably occurs by an uninfected devil biting into the tumour of an infected devil (Hamede et al., 2013), and that socially dominant devils do most of the biting. The model also suggested that the force of infection at West Pencil Pine has declined in the last 3–5 years (Wells et al., 2017). Whether this is evidence of evolution of resistance or simply a consequence of fewer susceptible devils being present in the population is unclear at present.

One important result of using tumour burden-dependent demographic functions is that time delays additional to those introduced by devil age structure and the latent period between exposure and infectiousness are introduced into the system. This means that DFTD epidemics operate on a much slower timescale than those of viral or bacterial wildlife diseases. It is possible that the dramatic increases in prevalence and declines in population size observed in the first five years following disease introduction (McCallum et al., 2009a) represent the initial peak of a classic epidemic curve (see Figure 11.5). Following an initial epidemic peak, the consequences for a general epidemic may be coexistence, usually after a series of diminishing subsequent epidemic peaks, fadeout of the infection, or (in a finite population or with frequency-dependent transmission) host extinction. These outcomes can occur in the absence of evolutionary changes in either host or the pathogen. It is too early to determine the likelihood of these outcomes in the case of Tasmanian devil facial tumour disease.

11.5 Evolution

In 2017, more than 20 years since the emergence of facial tumour disease, DFTD has spread across 95% of the distributional range of the devil (Figure 11.2) and caused more than 80% population decline (Lazenby et al. 2018), with local declines of more than 94% (Lachish et al., 2007). Yet, devils still persist at low density at the longest diseased sites, Freycinet and wukalina/Mt William, and there has been no further population decline since 2008 (Figure 11.2). This raises the possibility of evolutionary adaptation to the disease.

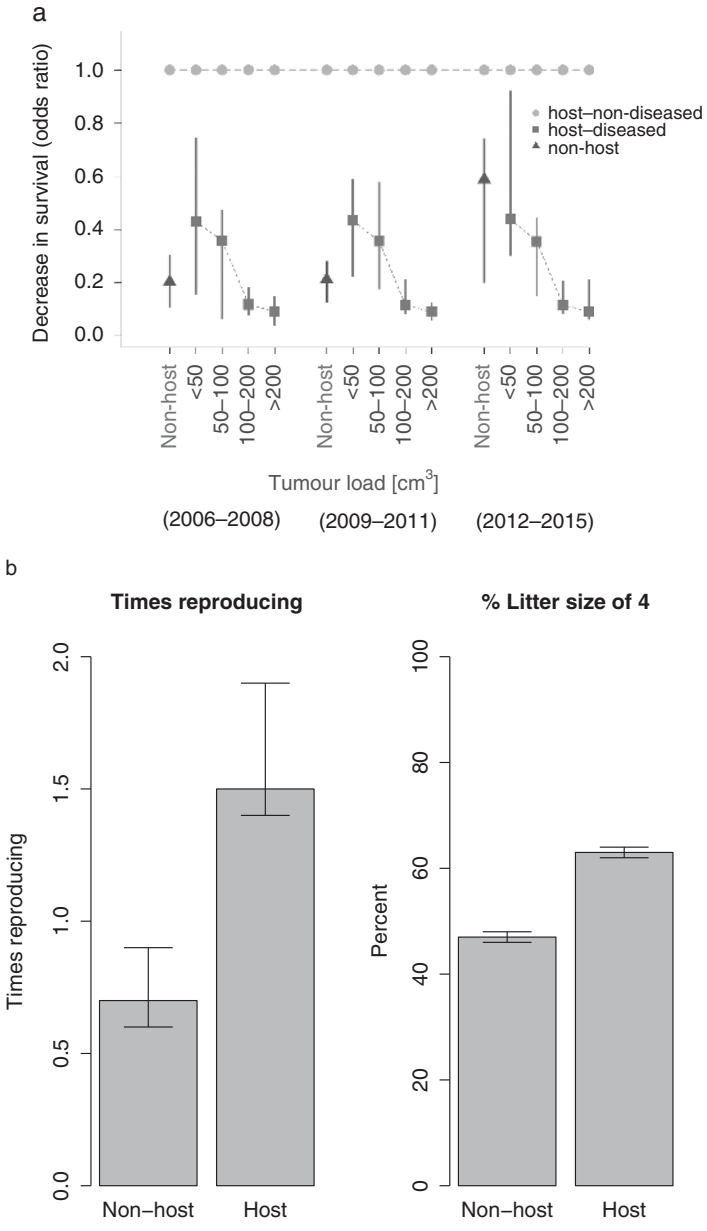

Figure 11.4 (A) Survival of Tasmanian devils at West Pencil Pine as a function of tumour load, for three time periods since disease arrival. Survival is shown as an odds ratio relative to that of non-diseased 'host' devils (from Wells et al., 2017). (B) Fecundity of Tasmanian devils at West Pencil Pine, for 'host' and non-host individuals, times reproducing and the percentage of litters of the maximum size of four (redrawn from Wells et al., 2017).

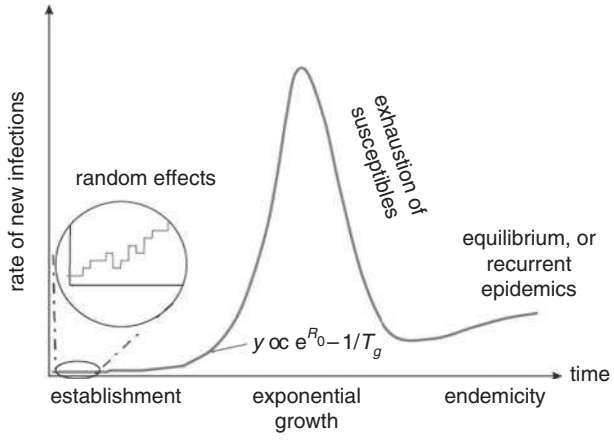

Figure 11.5 Idealised epidemic curve (Anderson et al., 2004). The early growth rate of the epidemic and the time until the epidemic peak are proportional to $(R_0 - 1)/T_g$ where R_0 is the basic reproductive rate and T_g is the generation time of the infection.

High mortality, typically associated with host naivety to emerging diseases (Roelke-Parker et al., 1996; Daszak et al., 2000; Robinson et al., 2010), places strong selective pressure on both host and pathogen. Evolution favours intermediate optimal virulence in pathogens to maximise transmission because pathogens that kill their host too fast can die out when virulence and transmission are inversely correlated (Ebert & Bull, 2003). Hosts can increase fitness by their individual abilities to avoid becoming infected (through, in the case of the Tasmanian devil, reduced aggression and biting behaviour), to resist or tolerate infection (Raberg et al., 2009), or to breed earlier to increase lifetime reproductive success (Jones et al., 2008). A dramatic reduction in aggressive behaviour towards handlers who measure and sample trapped devils suggests possible reduction in natural biting behaviour necessary for transmission (Dewar, 2013) that warrants further investigation. Plasticity in age at first breeding is within the devil's biology and is probably a response to better nutrition and faster juvenile growth rates following population decline in diseased areas (Lachish et al., 2009). In disease-free populations, most females first breed at age two and rarely at age one. Following disease-induced population decline, there has been a 16-fold increase in females that breed as one-year-old subadults (Jones et al., 2008). That only 50% of female devils can breed in their first year of independent life suggests that maternal effects, associated with the disease or precocial breeding status of the mother, and genetics may play a role (Lachish et al., 2009).

Multiple lines of evidence have shown that Tasmanian devils are evolving in response to DFTD. Using a time series of genome scan analyses across three populations (Freycinet, West Pencil Pine, Narawntapu; Figure 11.2) before and

after disease emergence, rapid evolution in a small number of candidate genes associated with cancer and immune function mapped to two genomic regions has been identified (Epstein et al., 2016). In addition, complete tumour regression has been documented in some individuals in the wild, along with antibody production (Pye et al., 2016a). Some of the individuals whose tumours regress survive to a healthy old age (six years). Other devils never become infected. Tumour regressions have been recorded across more than half of the devil's range in Tasmania (from a site to the west of West Pencil Pine to wukalina/Mt William in the north-east; Ruiz-Aravena, 2019). At a population level, the recent decline in the force of infection and transmission rate (Wells et al., 2017) is consistent with evolution of resistance, but may simply be a consequence of change in the number of susceptible devils in the population.

Disease tolerance might manifest as greater ability to withstand a given pathogen or tumour burden. If this led to longer survival, lifetime reproductive success and fitness may be increased. The detailed devil–DFTD epidemiological data from West Pencil Pine does not indicate that the relationship between tumour size and mortality has changed over 10 years (Figure 11.4A), although these results are confounded with unknown effects on mortality of a change in the dominant tumour karyotype from a tetraploid to diploid karyotype (Hamede et al., 2015). Variation in the ability of individual devils to maintain body condition in the face of increasing tumour burden does suggest the potential for natural selection to operate in wild devils in favour of tolerance to DFTD (Ruiz-Aravena et al., 2018).

The tumour is also evolving, with multiple lineages emerging and changing through space and time, evident in karyotypes (Pearse et al., 2012) and in the genome (Murchison et al., 2012). Tumour ploidy is associated with different epidemic and demographic effects, with tetraploid tumours having a slower impact on devils than diploid tumours, which grow to a larger final size (Hamede et al., 2015, 2017). The CTVT emerged about 11,000 years ago and is now an evolutionary stable cell line (Murgia et al., 2006; Murchison, 2008) (Box 11.1). The possibility that the tumour and the devil will interact in a coevolutionary selection environment is yet to be explored.

The next step in the data analysis is to determine whether the putative resistance alleles identified by Epstein et al. (2016) are associated with either reduced propensity to become infected, slower tumour growth rate, or increased survival with a given tumour burden, parameters that might indicate resistance. Using the integral projection model framework, implemented through an individual-based stochastic model, long-term evolutionary trajectories for the tumour–devil interaction can be projected. An unsolved challenge is that, while behavioural characteristics such as aggressiveness and dominance appeared to be strongly associated with propensity to become infected, there is little information on the heritability of such characteristics.

11.6 Future directions

Host extinction was predicted as a real possibility in the first decade of the epidemic when population growth rate was halving annually (McCallum et al., 2009), but now appears an unlikely outcome for the Tasmanian devil–facial tumour interaction. The research detailed here is directly responsible for a shift in conservation policy from managing for extinction to managing for persistence. Unanswered questions concern the nature of evolution and potentially coevolution, and whether and how rapidly population recovery in the wild might occur. The transmissible cancer in dogs, CTVT, remains a stable cell line after about 11,000 years of evolution (Murchison et al., 2014). The rapidity of the evolutionary response in devils is remarkable, particularly given the low genetic diversity in Tasmanian devil populations (Jones et al., 2004). Significant shifts in allele frequency at functional genes associated with immune function and cancer regulation have been documented in just 4–6 generations (8–12 years). This is much faster than the 20 generations over which evolutionary responses in the European rabbit (*Oryctolagus cuniculus*) occurred in response to the myxoma virus that was introduced as a biocontrol agent (Kerr et al., 2015).

The rapidity of the evolutionary response of the devil to DFTD suggests that selection is operating on standing genetic variation, genetic diversity that was present at the time of disease emergence (Epstein et al., 2016). Despite significant loss of genetic diversity correlating with environmental changes around the last glacial maximum, and following unstable climate related to increased 'El Ninõ–Southern Oscillation' activity approximately 2000–4000 years ago (Brüniche-Olsen et al., 2014), it appears that devils have sufficient adaptive capacity to survive this novel disease challenge. Genetic rescue (Frankham et al., 2017) via mixing genetic subpopulations may increase the overall genetic diversity of the species and possibly increase resilience to future disease challenges, as it has done in the Florida panther (Pimm et al., 2006). However, releasing animals from the insurance populations into long-infected areas where evolution has been an ongoing process may also dilute the evolutionary response to the disease and cause outbreeding depression (Frankham et al., 2011). In addition, there is a welfare issue, as these animals will be susceptible to DFTD. The inclusion of orphaned devils from the diseased eastern parts of Tasmania into the insurance population is helpful in capturing genetic variation that has evolved in response to the disease epidemic, but knowledge of the evolutionary changes at the genome level are preliminary. In addition, genetic rescue needs to be done in an adaptive management framework, with a monitoring programme sufficient to measure the outcome of the releases for disease and population dynamics.

A burning question is how evolution could be facilitated towards desirable outcomes, such as population recovery of devils and endemism of DFTD, using the knowledge being generated about the host and pathogen evolutionary

response. There are two potentially conflicting approaches here: managing for higher overall genetic diversity in the host, which may confer resilience to future diseases, and managing for locally adapted host resistance. While selective breeding for pathogen resistance has its place (le Roex et al., 2015), it can result in reduced genetic diversity and is not part of genetic rescue programmes which are frequently implemented for species with critically low genetic diversity (Frankham et al., 2017).

An important recent development in the Tasmanian devil–DFTD host–pathogen system is the emergence of a second transmissible cancer in this species (Pye et al., 2016b) (Box 11.1). This second cancer, named devil facial tumour 2 (DFT2), is a transmissible cancer which is grossly indistinguishable from DFTD (which has now been renamed DFT1). However, DFT2 tumours are histologically, cytogenetically, and genetically distinct from those caused by DFT1, indicating that DFT2 emerged independently. First observed in 2014, to date DFT2 has only been observed in a peninsula in south-east Tasmania. The emergence of DFT2 suggests that, although rare in nature, transmissible cancers may arise relatively frequently in Tasmanian devils. Thus, transmissible cancer epidemics such as that caused by DFT1 may have occurred in the past. It will be important to further address the nature of transmissible cancers in Tasmanian devils via comparative studies of DFT1 and DFT2.

Transmissible cancers are unusual pathogens (Box 11.1). Only eight naturally occurring transmissible cancers have been observed in nature: outside of DFT1 and DFT2 in Tasmanian devils, the only other naturally occurring transmissible cancer known in mammals is the 11,000-year-old CTVT (Murgia et al., 2006). The remaining five known transmissible cancers all cause leukaemia-like diseases in various species of marine bivalve molluscs (Metzger et al., 2015, 2016). Given that cancers which remain in a single host are relatively common – both in humans and in other species – the rarity of transmissible cancers suggests that cancers are unlikely to spread between hosts. This may be due to lack of transmission opportunities, or failure of incipient cancer clones to adapt to growth in allogeneic hosts. Indeed, it has been suggested that the genetic diversity of the MHC, the molecular system responsible for allograft detection, may have emerged in part due to selective pressures imposed by transmissible cancers (Murgia et al., 2006).

A big question is the future of transmissible cancers. Are we likely to see a burgeoning of new transmissible cancers in wildlife, livestock, or even humans? Are there environmental links to the emergence of new transmissible cancers, or are we just detecting more cases? Tasmanian devils have produced two different transmissible cancers in a 20-year period (Pye et al., 2016b) and three new cases were reported recently in invertebrates (Metzger et al., 2016). What is the prognosis for DFT2 and how will it interact or compete with DFT1?

Future benefits of research on the Tasmanian devil–facial tumour system will be theoretical advances in knowledge of the ecology and evolution of emerging infectious diseases in wildlife and their application to conservation. Integrating field data with genomics and mathematical models promises greater understanding of transmissible cancers and emerging infectious diseases in general, and of the epidemic and evolutionary outcomes of infectious diseases in wildlife. Specifically, integrating research on rapid evolution and potentially coevolution of host and tumour with epidemiological models will allow prediction of the potential persistence, recovery or extinction of the devil and this knowledge should guide conservation programmes such as translocations.

The potential for trophic cascades (Jones et al., 2007) following the decline and probable functional extinction (Hollings et al., 2015) of the devil over much of its range has been realised (Hollings et al., 2014, 2016). Until recently, the island of Tasmania had escaped the widespread declines and extinctions of mammals that occurred over most of the Australian mainland in the 150 years following European settlement (Woinarski et al., 2014). This can be attributed in large part to the failure of red foxes (*Vulpes vulpes*) to establish in Tasmania at that time, which is itself attributed to suppression by abundant devil populations. Tasmania's mammal community is now shifting towards domination by invasive species, with competitive release of feral cats (*Felis catus*) and expanding black rat (*Rattus rattus*) populations (Hollings et al., 2016) causing ecological changes mirroring those that occurred on the Australian mainland. Feral cats (*Felis catus*) are now considered to be the greatest threat to wildlife in Australia (Woinarski et al., 2014, 2015). At least 16 species of Tasmanian wildlife are at risk from increased cat predation; one of these, the Tasmanian subspecies of the New Holland mouse (*Pseudomys novaehollandiae*), may be on the brink of extinction (Lazenby, 2009). Direct control of feral cat populations, which relies on traditional lethal methods, is ineffective at large spatial scales (Doherty et al., 2017). Reversing the ecological damage by feral cats may be dependent on the eventual recovery of the devil.

11.7 Conclusions

Tasmanian devils, the world's largest marsupial carnivore and apex predator in Tasmania's ecosystems, have spawned two unusual pathogens – transmissible cancers – in a 20-year period. Despite their reasonably low genetic diversity, devils have responded with rapid evolution in resistance and potentially tolerance to this highly lethal epidemic disease. Proximity-sensing loggers on radiocollars to construct contact histories is useful in understanding transmission. Combining genomic analysis of evolution of both host and pathogen with state space and integral projection models, facilitated by large collections of field data and host and tumour genetic samples from multiple sites that span disease outbreak, may allow prediction of the likely epidemic outcome.

11.8 Acknowledgements

Research was funded by grants from the Australian Research Council (ARC Large Grant A00000162 to MJ, Linkage LP0561120 to MJ and HM, Linkage LP0989613 to MJ and EM, Discovery DP110102656 to MJ and HM), the US National Science Foundation (NSF DEB 1316549 to AS, PAH, MJ and HM), Eric Guiler grants from the Save the Tasmanian Devil Appeal – University of Tasmania Foundation, the Ian Potter Foundation, the Australian Academy of Science (Margaret Middleton Fund), Estate of WV Scott, the National Geographic Society, the Mohammed bin Zayed Conservation Fund, and the Holsworth Wildlife Trust. MJ received support from an ARC Future Fellowship (FT100100250) and a Fulbright Tasmania Senior Scholarship, RH from an ARC DECRA, AS as a Fulbright Senior Scholarship and Hamish McCallum as the Senior Scientist of the Save the Tasmanian Devil Program. MJ and HM were awarded an Australian Museum Eureka Prize – Sherman Prize for Environmental Science in 2011 for their contributions. MJ received the Australian Geographic Conservation Award in 2005 for contributions to the conservation of the Tasmanian devil. We acknowledge the many students who carried out different parts of this work, in particular Shelly Lachish, Nick Beeton, Sebastien Comte, David Hamilton, and Manuel Ruiz. We thank the Public Library of Science, Biology for permission to reproduce Figure 11.3 under their CC-BY copyright licence. The research was carried out under Animal Ethics approvals from the University of Tasmania and Scientific Permits from the Tasmanian Department of Primary Industry, Parks, Water and Environment.

References

Altizer, S., Nunn, C.L., Thrall, P.H., et al. (2003) Social organization and parasite risk in mammals: integrating theory and empirical studies. *Annual Review of Ecology Evolution and Systematics*, **34**, 517–547.

Anderson, R.M., Fraser, C., Ghani, A.C., et al. (2004). Epidemiology, transmission dynamics and control of SARS: the 2002–2003 epidemic. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences*, **359**, 1091–1105.

Anderson, R.M. & May, R.M. (1979) Population biology of infectious diseases. Part I. *Nature*, **280**, 361–367.

AusVet. (2005) Tasmanian devil facial tumour disease response. Technical Workshop: 29–31 August 2005. Hobart (Tasmania): Department of Primary Industries, Water, and Environment.

Beeton, N. (2011) Population and disease modelling in the Tasmanian devil. PhD thesis, University of Tasmania.

Beeton, N. & McCallum, H. (2011) Models predict that culling is not a feasible strategy to prevent extinction of Tasmanian devils from facial tumour disease. *Journal of Applied Ecology*, **48**, 1315–1323.

Brown, G.K., Tovar, C., Cooray, A.A., et al. (2016) Mitogen-activated Tasmanian devil blood mononuclear cells kill devil facial tumour disease cells. *Immunology and Cell Biology*, **94**, 673–679.

Bruniche-Olsen, A., Jones, M.E., Austin, J.J., Burridge, C.P. & Holland, B.R. (2014) Extensive population decline in the Tasmanian devil predates European settlement and Devil Facial Tumor Disease. *Biology Letters*, **10**, 20140619.

Burgman, M.A. (2005) *Risks and Decisions for Conservation and Environmental Management*. New York, NY: Cambridge University Press.

Coulson, T. (2012) Integral projections models, their construction and use in posing hypotheses in ecology. *Oikos*, **121**, 1337–1350.

Daszak, P., Cunningham, A.A. & Hyatt, A.D. (2000) Emerging infectious diseases of wildlife – threats to biodiversity and human health. *Science*, **287**, 443–449.

De Castro, F. & Bolker, B. (2005) Mechanisms of disease-induced extinction. *Ecology Letters*, **8**, 117–126.

Dewar, E. (2013) Understanding behaviour, stress and disease in Tasmanian devils: implications for selective adaptations. Honours thesis, University of Tasmania.

Doherty, T.S., Dickman, C.R., Johnson, C.N., et al. (2017) Impacts and management of feral cats *Felis catus* in Australia. *Mammal Review*, **47**(2), 83–97. https://doi.org/10.1111/mam.12080

Donnelly, C.A., Ghani, A.C., Leung, G.M., et al. (2003) Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *The Lancet*, **361**, 1761–1766.

Easterling, M.R., Ellner, S.P. & Dixon, P.M. (2000) Size-specific sensitivity: applying a new structured population model. *Ecology*, **81**, 694–708.

Ebert, D. & Bull, J.J. (2003) Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends in Microbiology*, **11**, 15–20.

Epstein, B., Jones, M., Hamede, R., et al. (2016) Rapid evolutionary response to a transmissible cancer in Tasmanian devils. *Nature Communications*, **7**, 12684.

Frankham, R. (2008) Genetic adaptation to captivity in species conservation programs. *Molecular Ecology*, **17**, 325–333.

Frankham, R., Ballou, J.D., Eldridge, M.D.B., et al. (2011) Predicting the probability of outbreeding depression. *Conservation Biology*, **25**, 465–475.

Frankham, R., Ballou, J.D., Ralls, K., et al. (2017) *Genetic Management of Fragmented Animal and Plant Populations*. Oxford: Oxford University Press.

Galvani, A.P. & May, R.M. (2005) Dimensions of superspreading. *Nature*, **438**, 293.

Hamede, R., Bashford, J., Jones, M. & McCallum, H. (2012) Simulating devil facial tumour disease outbreaks across empirically derived contact networks. *Journal of Applied Ecology*, **49**, 447–456.

Hamede, R.K., Bashford, J., McCallum, H. & Jones, M. (2009) Contact networks in a wild Tasmanian devil (*Sarcophilus harrisii*) population: using social network analysis to reveal seasonal variability in social behaviour and its implications for transmission of devil facial tumour disease. *Ecology Letters*, **12**, 1147–1157.

Hamede, R.K., Beeton, N.J., Carver, S. & Jones, M. E. (2017) Untangling the model muddle: empirical tumour growth in Tasmanian devil facial tumour disease. *Scientific Reports*, **7**(1), 6217.

Hamede, R.K., McCallum, H. & Jones, M. (2008) Seasonal, demographic and density-related patterns of contact between Tasmanian devils (*Sarcophilus harrisii*): implications for transmission of devil facial tumour disease. *Austral Ecology*, **33**, 614–614.

Hamede, R.K., McCallum, H. & Jones, M. (2013) Biting injuries and transmission of Tasmanian devil facial tumour disease. *Journal of Animal Ecology*, **82**, 182–190.

Hamede, R.K., Pearse, A.M., Swift, K., Barmuta, L.A., Murchison, E.P. & Jones, M. E. (2015) Transmissible cancer in Tasmanian devils: localized lineage replacement and host population response. *Proceedings of the Royal Society of London B*, **282**, 20151468.

Hawkins, C.E., Baars, C., Hesterman, H., et al. (2006) Emerging disease and population decline of an island endemic, the Tasmanian devil *Sarcophilus harrisii*. *Biological Conservation*, **131**, 307–324.

Hawkins, C.E., McCallum, H., Mooney, N., Jones, M. & Holdsworth, M. (2009) *Sarcophilus harrisii*. IUCN Red List of threatened species. Version **2009**. 1.

Hollings, T., Jones, M., Mooney, N. & McCallum, H. (2014) Trophic cascades following the disease-induced decline of an apex predator, the Tasmanian devil. *Conservation Biology*, **28**, 36–75.

Hollings, T., Jones, M., Mooney, N. & McCallum, H. (2016) Disease-induced decline of an apex predator drives invasive dominated states and threatens biodiversity. *Ecology*, **97**, 394–405.

Hollings, T., McCallum, H., Kreger, K., Mooney, N. & Jones, M. (2015) Relaxation of risk-sensitive behaviour of prey following disease-induced decline of an apex predator, the Tasmanian devil. *Proceedings of the Royal Society of London B*, **282**, 20150124.

Huxtable, S.J., Lee, D.V., Wise, P. & Save the Tasmanian Devil Program. (2015) Metapopulation management of an extreme disease scenario. In: Armstrong, D. P., Hayward, M.W., Moro, D. & Seddon, B.P. (eds.), *Advances in Reintroduction Biology of Australian and New Zealand Fauna.* Clayton, Victoria, Australia: CSIRO.

Jones, M.E. (2003) Convergence in ecomorphology and guild structure among marsupial and placental carnivores. In: Jones, M.E., Dickman, C.R. & Archer, M. (eds.), *Predators With Pouches: The Biology of Carnivorous Marsupials*. Melbourne, Australia: CSIRO Publishing.

Jones, M.E., Cockburn, A., Hamede, R., et al. (2008) Life-history change in disease-ravaged Tasmanian devil populations. *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 10,023–10,027.

Jones, M.E., Jarman, P.J., Lees, C.M., et al. (2007) Conservation management of Tasmanian devils in the context of an emerging, extinction-threatening disease: devil facial tumor disease. *EcoHealth*, **4**, 326–337.

Jones, M.E., Paetkau, D., Geffen, E.L.I. & Moritz, C. (2004) Genetic diversity and population structure of Tasmanian devils, the largest marsupial carnivore. *Molecular Ecology*, **13**, 2197–2209.

Karu, N., Wilson, R., Hamede, R., et al. (2016) Discovery of biomarkers for Tasmanian devil cancer (DFTD) by metabolic profiling of serum. *Journal of Proteome Research*, **15**, 3827–3840.

Kerr, P. J., Liu, J., Cattadori, I., et al. (2015) Myxoma virus and the leporipoxviruses: an evolutionary paradigm. *Viruses*, **7**, 1020–1061.

Kreiss, A., Brown, G.K., Tovara, C., Lyons, A. B. & Woods, G.M. (2015). Evidence for induction of humoral and cytotoxic immune responses against devil facial tumor disease cells in Tasmanian devils *Sarcophilus harrisii* immunized with killed cell preparations. *Vaccine*, **33**, 3016–3025.

Lachish, S., Jones, M. & McCallum, H. (2007) The impact of disease on the survival and population growth rate of the Tasmanian devil. *Journal of Animal Ecology*, **76**, 926–936.

Lachish, S., McCallum, H. & Jones, M. (2009) Demography, disease and the devil: life-history changes in a disease-affected population of Tasmanian devils (*Sarcophilus harrisii*). *Journal of Animal Ecology*, **78**, 427–436.

Lachish, S., McCallum, H., Mann, D., Pukk, C. & Jones, M.E. (2010) Evaluation of selective culling of infected individuals to control Tasmanian devil facial tumor disease. *Conservation Biology*, **24**, 841–851.

Lafferty, K.D. & Kuris, A.M. (2002) Trophic strategies, animal diversity and body size. *Trends in Ecology & Evolution*, **17**, 507–513.

Lazenby, B. (2009) Habitat identification and hair tube surveys for the Endangered New Holland Mouse in Tasmania with a focus on the St Helens area. www .northeastbioregionalnetwork.org.au/docs/NEBN%20final%20report.pdf (downloaded 08/06/2017): North East Bioregional Network.

Lazenby, B.T., Tobler, M.W., Brown, W.E., et al. (2018) Density trends and demographic signals uncover the long-term impact of transmissible cancer in Tasmanian devils. *Journal of Applied Ecology*, **55**, 1368–1379. https://doi.org/10.1111/1365–2664.13088

Le Roex, N., Berrington, C.M., Hoal, E.G. & Van Helden, P.D. (2015) Selective breeding: the future of TB management in African buffalo? *Acta Tropica*, **149**, 38–44.

Lloyd-Smith, J.O., Schreiber, S.J., Kopp, P.E. & Getz, W.M. (2005) Superspreading and the effect of individual variation on disease emergence. *Nature*, **438**, 355–359.

May, R.M. & Anderson, R. M. (1979) Population biology of infectious diseases. Part II. *Nature*, **280**, 455–461.

McCallum, H. (2005) Inconclusiveness of chytridiomycosis as the agent in

widespread frog declines. *Conservation Biology*, **19**, 1421–1430.

McCallum, H. & Jones, M. (2006) To lose both would look like carelessness: Tasmanian devil facial tumour disease. *PLoS Biology*, **4**, e342–1674.

McCallum, H. & Jones, M. (2010) Sins of omission and sins of commission: St Thomas Aquinas and the devil. *Australian Zoologist*, **35**, 307–314.

McCallum, H. & Jones, M. (2012) Infectious cancer in wildlife. In: Aguirre, A., Daszak, P. & Ostfeld, R. (eds.), *Conservation Medicine: Applied Cases of Ecological Health* (pp. 270–283). Oxford: Oxford University Press.

McCallum, H., Jones, M., Hawkins, C., et al. (2009) Transmission dynamics of Tasmanian devil facial tumor disease may lead to disease-induced extinction. *Ecology*, **90**, 3379–3392.

Metcalf, C.J.E., Graham, A.L., Martinez-Bakker, M. & Childs, D.Z. (2016) Opportunities and challenges of Integral Projection Models for modelling host–parasite dynamics. *Journal of Animal Ecology*, **85**, 343–355.

Metzger, M.J., Reinisch, C., Sherry, J. & Goff, S.P. (2015) Horizontal transmission of clonal cancer cells causes leukemia in soft-shell clams. *Cell*, **161**, 255–263.

Metzger, M.J., Villalba, A., Carballal, M.J., et al. (2016) Widespread transmission of independent cancer lineages within multiple bivalve species. *Nature*, **534**, 705–709.

Mooney, N. (2004) The devil's new hell. *Nature Australia*, **28**, 34.

Murchison, E.P. (2008) Clonally transmissible cancers in dogs and Tasmanian devils. *Oncogene*, **27**, S19–S30.

Murchison, E.P., Schulz-Trieglaff, O.B., Ning, Z., et al. (2012) Genome sequencing and analysis of the Tasmanian devil and its transmissible cancer. *Cell*, **148**, 780–791.

Murchison, E.P., Wedge, D.C., Alexandrov, L. B., et al. (2014) Transmissable dog cancer genome reveals the origin and history of an ancient cell lineage. *Science*, **343**, 437–440.

Murgia, C., Pritchard, J.K., Kim, S.Y., Fassati, A. & Weiss, R.A. (2006) Clonal origin and evolution of a transmissible cancer. *Cell*, **126**, 477–487.

Nak, D., Nak, Y., Cangul, I.T. & Tuna, B. (2005) A clinico-pathological study on the effect of vincristine on transmissible venereal tumour in dogs. *Journal of Veterinary Medicine Series A*, **52**, 366–370.

Pearse, A.M. & Swift, K. (2006) Transmission of devil facial-tumour disease – an uncanny similarity in the karyotype of these malignant tumours means that they could be infective. *Nature*, **439**, 549–549.

Pearse, A.M., Swift, K., Hodson, P., et al. (2012) Evolution in a transmissible cancer: a study of the chromosomal changes in devil facial tumor (DFT) as it spreads through the wild Tasmanian devil population. *Cancer Genetics*, **205**, 101–112.

Phalen, D.N., Frimberger, A., Pyecroft, S., et al. (2013) Vincristine chemotherapy trials and pharmacokinetics in Tasmanian devils with Tasmanian devil facial tumor disease. *PLoS ONE*, **8**, e65133.

Phalen, D.N., Frimberger, A.E., Peck, S., et al. (2015) Doxorubicin and carboplatin trials in Tasmanian devils (*Sarcophilus harrisii*) with Tasmanian devil facial tumor disease. *The Veterinary Journal*, **206**, 312–316.

Pimm, S.L., Dollar, L. & Bass Jr, O.L. (2006) The genetic rescue of the Florida panther. *Animal Conservation*, **9**, 115–122.

Pye, R., Hamede, R., Siddle, H., et al. (2016a) Demonstration of immune responses against devil facial tumour disease in wild Tasmanian devils. *Biology Letters*, **12**, 20160553.

Pye, R.J., Pemberton, D., Tovar, C., et al. (2016b) A second transmissible cancer in Tasmanian devils. *Proceedings of the National Academy of Sciences of the United States of America*, **113**, 374–379.

Pyecroft, S.B., Pearse, A.M., Loh, R., et al. (2007) Towards a case definition for devil facial tumour disease: what is it? *EcoHealth*, **4**, 346–351.

Raberg, L., Graham, A.L. & Read, A.F. (2009) Decomposing health: tolerance and resistance to parasites in animals. *Philosophical Transactions of the Royal Society of London B*, **364**, 37–49.

Robinson, A.C., Lawson, B., Toms, M.P., et al. (2010) Emerging infectious disease leads to rapid population declines of common British birds. *PLoS ONE*, **5**, e12215.

Roelke-Parker, M.E., Munson, L., Packer, C., et al. (1996) A canine distemper virus epidemic in Serengeti lions (*Panthera leo*). *Nature*, **379**, 441–445.

Rogers, T., Fox, S., Pemberton, D. & Wise, P. (2016) Sympathy for the devil: captive-management style did not influence survival, body-mass change or diet of Tasmanian devils 1 year after wild release. *Wildlife Research*, **43**, 544–552.

Ruiz-Aravena, M. (2019). The Tasmanian devil and its transmissible cancer: physiology of the devil-DFTD interaction. PhD thesis, University of Tasmania.

Ruiz-Aravena, M., Jones, M.E., Carver, S., et al. (2018). Sex bias in ability to cope with cancer: Tasmanian devils and facial tumour disease. *Proceedings of the Royal Society of London B*, **285**, 20182239.

Sakai, A.K., Allendorf, F.W., Holt, J.S., et al. (2001) The population biology of invasive species. *Annual Review of Ecology and Systematics*, **32**, 305–332.

Scudamore, J.M. & Harris, D.M. (2002) Control of foot and mouth disease: lessons from the experience of the outbreak in Great Britain in 2001. *Revue scientifique et technique (International Office of Epizootics)*, **21**, 699–710.

Siddle, H.V., Kreiss, A., Tovar, C., et al. (2013) Reversible epigenetic down-regulation of MHC molecules by devil facial tumour disease illustrates immune escape by a contagious cancer. *Proceedings of the National Academy of Sciences of the United States of America*, **110**, 5103–5108.

Tompkins, D.M., Carver, S., Jones, M.E., Krkosek, M. & Skerratt, L.F. (2015) Emerging infectious diseases of wildlife: a critical perspective. *Trends in Parasitology*, **31**, 149–159.

Tovar, C., Obendorf, D., Murchison, E.P., et al. (2011) Tumor-specific diagnostic marker for transmissible facial tumors of Tasmanian devils: immunohistochemistry studies. *Veterinary Pathology*, **48**, 1195–1203.

Wayne, R.K., Geffen, E., Girman, D.J., et al. (1997) Molecular systematics of the Canidae. *Systematic Biology*, **46**, 622–653.

Wells, K., Hamede, R.K., Kerlin, D.H., et al. (2017a) Infection of the fittest: devil facial tumour disease has greatest effect on individuals with highest reproductive output. *Ecology Letters*, **20**, 770–778.

Wilber, M.Q., Langwig, K.E., Kilpatrick, A.M., McCallum, H.I. & Briggs, C.J. (2016) Integral Projection Models for host–parasite systems with an application to amphibian chytrid fungus. *Methods in Ecology and Evolution*, **7**, 1182–1194.

Woinarski, J.C., Burbidge, A.A. & Harrison, P.L. (2015) Ongoing unraveling of a continental fauna: decline and extinction of Australian mammals since European settlement. *Proceedings of the National Academy of Sciences of the United States of America*, **112**, 4531–4540.

Woinarski, J.C.Z., Burbidge, A.A. & Harrison, P.L. (2014) *The Action Plan for Australian Mammals 2012*. Melbourne, Australia: CSIRO Publishing.

Woods, G.M., Howson, L.J., Brown, G.K., et al. (2015) Immunology of a transmissible cancer spreading among Tasmanian devils. *The Journal of Immunology*, **195**, 23–29.