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Infection of the fittest: devil facial tumour disease has greatest effect on individuals with highest reproductive output

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25 **Running head: Host fitness and transmissible cancer**

26

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40 **Abstract**

41 Emerging infectious diseases rarely affect all members of a population equally and
42 determining how individuals' susceptibility to infection is related to other components of
43 their fitness is critical to understanding disease impacts at a population level and for
44 predicting evolutionary trajectories. We introduce a novel state-space model framework to
45 investigate survival and fecundity of Tasmanian devils (*Sarcophilus harrisi*) affected by a
46 transmissible cancer, devil facial tumour disease. We show that those devils that become host
47 to tumours have otherwise greater fitness, with higher survival and fecundity rates prior to
48 disease induced death than non-host individuals that do not become infected, although high

49 tumour loads lead to high mortality. Our finding that individuals with the greatest
50 reproductive value are those most affected by the cancer demonstrates the need to quantify
51 both survival and fecundity in context of disease progression for understanding the impact of
52 disease on wildlife populations.

53

54 **INTRODUCTION**

55 Infectious diseases rarely affect all individuals in a population equally (Grenfell *et al.* 2001;
56 Lloyd-Smith *et al.* 2005). In many cases, it is the weakest, least fit, members of a population
57 that are most impacted by pathogens. Low-ranking individuals or those in overcrowded
58 aggregations have been reported to exhibit lower immune function and higher disease risk
59 owing to a range of factors that can influence survival and fecundity (Sapolsky 2004).
60 Conversely, dominant individuals that typically engage in mating and reproduction more
61 frequently than subordinates, may trade off energetic investment in reproduction at the
62 expense of immune-competence, ultimately increasing their disease risk (Sheldon & Verhulst
63 1996; Lee 2006; Sepil *et al.* 2013). In either case, higher infection risk is frequently reported
64 in association with stress and immune-suppression, implying that the infection of relatively
65 weakened individuals is common-place in disease spread and persistence (Beldomenico &
66 Begon 2010).

67 Predicting the effects of infectious diseases on populations remains challenging due to
68 the intricate interplay of demographic and epidemiological dynamics (Merler & Ajelli 2010;
69 Peel *et al.* 2014). High disease-induced mortality, for example, does not necessarily imply
70 decline in population growth if increased fecundity can compensate for the loss at the
71 population-level (Wells *et al.* 2015), and/or if surviving individuals benefit from increased
72 survival or reproductive opportunities due to decreased competition (Gaillard *et al.* 2000;

73 Coulson *et al.* 2004). Hence, the consequences of disease outbreaks at the population-level
74 ultimately depend on individual fitness outcomes, that is, the relative reproductive potential
75 of individuals that become host to the disease and non-host individuals, i.e. those individuals
76 never affected by the disease. If, for example, a disease mainly affects individuals that are
77 unlikely to contribute to recruitment (e.g. post-reproductive individuals), even a highly lethal
78 disease would have little effect on long-term population growth (see **Fig. 1**). If, however, the
79 disease impacts those individuals most likely to contribute to recruitment then disease effects
80 on population growth may be more substantial.

81 Here, we examine the fitness consequences of devil facial tumour disease (DFTD) for
82 Tasmanian devils (*Sarcophilus harrisii*) using 10 years of mark-recapture data. DFTD is a
83 recently emerged infectious disease caused by a clonal cancer, transmitted by direct transfer
84 of live cancer cells when devils bite each other (Hawkins *et al.* 2006; Pearse & Swift 2006;
85 Jones *et al.* 2008; Hamede *et al.* 2013). DFTD is mostly fatal, with large ulcerating tumours
86 leading to metabolic starvation, overgrown oral cavities or organ failure resulting from
87 metastasis. High contact rates among individuals, often resulting in aggressive interactions
88 including biting, and frequency-dependent disease transmission have been expected to reduce
89 devil populations to very low levels (Lachish *et al.* 2007; Hamede *et al.* 2009; McCallum *et*
90 *al.* 2009). In contrast, precocial reproduction of devils when the cancer reduces population
91 density and hence intraspecific competition has been suggested as an adaptive host
92 mechanism (Jones *et al.* 2008; Lachish *et al.* 2009). However, the extent to which individuals
93 that become host to the cancer exhibit different fitness compared to non-host individuals that
94 never become infected, and the timing and extent of reproduction in relation to individual
95 disease status has not been examined so far. In order to explore fitness in the context of
96 individual and population-level disease progression we developed a novel state-space model

97 framework that integrates individual-based survival and fecundity in the context of disease
98 progression and epidemiological dynamics over time.

99

100 **METHODS**

101 **Study system and field data**

102 We analysed mark-recapture data from individually marked Tasmanian devils collected
103 between July 2006 and November 2015 from a population in western Tasmania (West Pencil
104 Pine, 41°31 S, 145°46 E) (Hamede *et al.* 2015). Devils were captured at three month intervals
105 ($93 \pm SD=18$ days between capture sessions). The timing of capture sessions coincided with
106 key reproductive stages during the annual cycle and were categorized into four seasons: 1)
107 February/March (mating season), 2) May (small pouch young), 3) July/August (large pouch
108 young), and 4) November (females are in late lactation with young in den). We further
109 categorized capture sessions into three 3–4 year time periods: 1) 2006–2008, 2) 2009–2011,
110 3) 2012–2015. As a compromise between exploring temporal variation and model
111 complexity, we chose these arbitrary intervals rather than fitting a continuous time function.
112 Shifts in tumour strain frequency (Hamede *et al.* 2015) and host genes related to immune
113 response (Epstein *et al.* 2016) could cause different DFTD effects on survival rates, but the
114 exact timing of relevant events are unknown. We classified the reproductive status of females
115 based on pouch appearance (Hesterman *et al.* 2008) into 6 categories: 1) immature, 2)
116 oestrous, 3) postovulatory, 4) pouch young presence, 5) lactating, 6) regressing teats. The
117 number of pouch young were counted if present. The size of each DFTD tumour detected was
118 measured with callipers to the nearest 1-5 mm in three dimensions (depth measurements of
119 tumours inside the skin were least accurate) and the per-capita tumour load (tumour volume
120 to the nearest cm^3) was calculated. Hamede *et al.* (2015) provides further descriptions of field
121 methods. See Supplementary Information for sample sizes.

122

123 Hierarchical model of individual fitness and disease progression*124 (1) Survival*

125 We used a Bayesian hierarchical mark-recapture model, in which we integrated an
126 incremental growth model of tumour load to project unknown disease states for all time steps
127 when diseased individuals were likely to be alive but tumour load was not known. We use
128 ‘tumour load’, the total volume of all tumours on an individual at a particular time, rather
129 than modelling each individual tumour separately because some tumours merged together
130 over time and not all tumours were distinguishable. We assume that tumour growth is
131 governed by an underlying ergodic and irreversible Markov process (once diseased,
132 individuals remain diseased until death and tumour load is assumed to continuously increase;
133 the rare events where shrinking tumours have been observed are modelled by the Gamma
134 process as described below). Our model resembles a continuous-time Markov chain model
135 for discrete state variables, and we projected all data on a continuous time scale (the first day
136 of the study set to one) in order to express the time of all events such as individual age,
137 lifetime and the onset of tumour growth as Euclidean temporal distances.

138 We used the term ‘host’ for all individuals that were known to harbour tumours at any
139 stage during their lifetime and the term ‘non-host’ for individuals never observed with
140 tumours during their lifetime. Host individuals were classified as ‘diseased’ if tumour were
141 present and as ‘non-diseased’ prior to the onset of tumour growth.

142 For each individual devil i , we noted the encounter at time t (the total number of
143 trapping sessions being T) as a binary vector Y_i of length T with $y(i,t) = 1$ if the individual is
144 encountered and $y(i,t) = 0$ otherwise. The capture records $y(i,t)$ are assumed to be random
145 observations of the true presence-absence $z(i,t)$ of individual i at time t based on capture
146 probability $p(i,t)$ with

$$147 \quad y(i,t) \sim \text{Bernoulli}(z(i,t)p(i,t)) \quad (1).$$

148 The incompletely known individual states $z(i,t)$ were estimated based on the survival
 149 probability $\Phi(i,t)$ conditioned that individuals were alive at the previous time step $t-1$ such
 150 that:

$$151 \quad z(i,t) \sim \text{Bernoulli}[\Phi(i,t)^{\delta(t)} z(i,t-1) I_{born}(i,t) (1 - I_{died}(i,t))] \quad (2).$$

152 The exponential scaling factor $\delta(t)$ accounts for unequal time intervals between capture
 153 sessions and was calculated as the ratio of the time interval between capture sessions to the
 154 average interval (93 days). The binary Boolean indicators $I_{born}(i,t)$ and $I_{died}(i,t)$ indicate
 155 whether individuals are born or have died at time step t (i.e. $I_{born}(i,t) = 1$ if already born and 0
 156 otherwise, $I_{died}(i,t) = 1$ if already dead and 0 otherwise), derived from the Markov chains of
 157 individual states. For most individuals the year of birth was known and uncertainty of the
 158 exact birth date fell into a 20-day window around the 1st April; for the few individuals with
 159 unknown birthdates (8 out of 518), uncertainty in birthdates was assumed to cover the time
 160 window of 6 years before first capture according to assumed maximum devil lifespan. For
 161 analysis, we drew individual birthdates $\Pi(i)$ as random variables from a uniform distribution
 162 across individual uncertainty intervals; given $\Pi(i)$ and $z(i,t)$, for any time the individual age
 163 can be calculated given the underlying Markov process.

164 We modelled survival probability $\Phi(i,t)$ based on *logit*-link functions as

$$165 \quad \text{logit}[\Phi(i,t)] = \mu_{\Phi}[\text{age}_{cat}(i,t), \text{period}(t)] + \beta_{sex}[\text{sex}(i)] + \beta_{host}[I_{host}(i)I_{age \geq 425d}(i,t)] + \\ 166 \quad \beta_{tumour}[\omega_{cat}(i,t), \text{period}(t)] + B_T X_T(t) \quad (3).$$

167 Here, μ_{Φ} is the intercept, which we allowed to vary among different age classes and time
 168 periods. We considered individual age as a categorical variable $\text{age}_{cat}(i,t)$ with six levels: 1) 1
 169 – 365 days, 2) 1 – 2 years, 3) 2 – 3 years, 4) 3 – 4 years, 4) 4 – 5 years, 5) > 5 years. The
 170 coefficient estimate β_{sex} captures variation in survival probability due to devil's sex. The
 171 coefficient β_{host} allows for variation in survival of mature host versus non-host individuals \geq

172 425 days old; we chose this threshold as this is the earliest age when individuals are expected
 173 to engage in reproduction and biting behaviour relevant for disease transmission (Jones *et al.*
 174 2008). The coefficient β_{tumour} captures variation in survival according to individual tumour
 175 load category $\omega_{cat}(i,t)$, based on categorizing tumour load $\omega(i,t)$ (see below) into four
 176 different levels: 1) $0.0001 - 50 \text{ cm}^3$, 2) $> 50 - 100 \text{ cm}^3$, 3) $> 100 - 200 \text{ cm}^3$, 4) $> 200 \text{ cm}^3$. X_T
 177 is a matrix of time steps ($t = 1, \dots, T$) of 4th orthogonal polynomial order (for modelling non-
 178 linear relationships), B_T is a vector of coefficient estimates for the polynomial model of the
 179 time covariate.

180 Capture probability $p(i,t)$ was modelled with a *logit*-link functions as

$$181 \quad \text{logit}[p(i,t)] = \mu_p(s) + \gamma_{infect}[I_{infect}(i,t)] + G_T X_T(t) \quad (4),$$

182 allowing the intercept to vary over season s , depending on whether individuals were diseased
 183 or not with DFTD at time t (as given by the Boolean indicator $I_{infect}(i,t)$), and as a polynomial
 184 function of time t of 4th order with coefficients G_T .

185

186 (2) Reproduction

187 We estimated the reproductive state of female f at time t as $\eta_{Repro}(f,t)$, which was
 188 unknown when individuals were not captured and pouch appearance could not be classified
 189 (note that the double-index notation $i[f]$ is used to match individuals i from the overall model
 190 framework to female f). Transition probabilities between the different reproductive states r
 191 can be summarized into an $R \times R$ matrix ($R=6$ for the six different reproductive stages) with
 192 marginal sums of one. We accounted for a directional transition between reproductive stages,
 193 i.e. the probability to be in any reproductive stage is conditioned on the previous states such
 194 that individuals once oestrous cannot become immature again but individuals can repeatedly
 195 reproduce once matured. We modelled reproductive states for each individual and time step
 196 based on the matrix of transition probabilities $\Psi(r_{current}, r_{future}, s, j)$; Ψ was allowed to vary

197 among seasons s and for host versus non-host individuals as indexed by j and was conditional
 198 on the individuals' previous reproductive state (using the sum to unity constraint of the
 199 multinomial distribution):

$$200 \quad \eta_{Repro}(f,t) \sim \text{Multinomial}[\Psi(\eta_{Repro}(f,t-1), R, s, j) z(i[f],t-1) + \Psi^0_{Repro}(R) (1 - z(i[f],t)) (1 \\ 201 - I_{died}(i[f],t))] \quad (5).$$

202 We used indicator variables to distinguish transition probabilities when individuals are alive
 203 ($z(i[f],t)=1$) from those prior to individual birth ($z(i[f],t)=0, I_{died}(i[f],t)=0$) in order to enforce
 204 the constraint that unborn individuals ($I_{born}(i[f],t)=0$) are in the immature state ($\Psi^0_{Repro}(R)$ is a
 205 vector of length R with the first value set to 1 and all others to 0).

206 For each year y a female was alive ($z(i[f],t)=1$), we calculated individual litter size $l(f,y)$ as
 207 the number of pouch young. Random state values of $l(f,y)$ were estimated based on the
 208 expected population-level probability $\pi(l,j)$ of the different litter sizes (with $l \in L$ indexing 1-
 209 4 young and $\sum_{l=1}^L \pi(l) = 1$) and conditional that an individual is expected to reproduce. We
 210 estimated $\pi(l,j)$ separately for host versus non-host individuals as indexed by j . The random
 211 variable $l(f,y)$ allowed us also to summarize the expected yearly population-level number of
 212 young. As part of preliminary analysis, we also allowed $\Psi(r_{current}, r_{future}, s, j)$ and $\pi(l,j)$ to vary
 213 for diseased versus non-diseased host individuals (i.e. the index j included an additional
 214 category conditioned on infection status); since results were similar we ignored this aspect in
 215 the final model to increase computational efficiency.

216

217 (3) Tumour incremental growth and projection

218 We fitted an incremental growth model to tumour load measurements $m(i,t)$ based on a
 219 logistic growth model which has been found to provide accurate fit to the growth of
 220 individual tumours (R.H. unpublished manuscript), and a Gamma process to account for
 221 random variation in each incremental growth step independent of the population-level mean

222 growth (Russo *et al.* 2009; Eaton & Link 2011). For this, we assumed field measures of
 223 tumour load $m(i,t)$ to be random draws from the underlying growth process over the time
 224 interval $t1$ and $t2$ between consecutive measurements such that

$$225 \quad m(i,t2) = \omega(i,t1) + \iota(i,t2) dt(t2) + \varepsilon_{\omega} \quad (6).$$

226 Here, $\omega(i, t1)$ is the tumour load at time step $t1$, $\iota(i, t2)dt(t2)$ is the product of the daily
 227 increment $\iota(i, t2)$ and the length of the time interval dt between $t1$ and $t2$, and ε_{ω} is random
 228 Gaussian noise. The increment $\iota(i, t2) = (\omega(i, t2) - \omega(i, t1))/ dt(t2)$ is assumed to be a Gamma
 229 random variable $\iota(i, t2) \sim \text{Gamma}(P(i, t2), \lambda)$ with shape parameter $P(i, t2)$ and scale
 230 parameter $\lambda > 0$. The shape parameter $P(i, t2)$ is based on the expected mean daily tumour
 231 growth according to the underlying logistic growth with

$$232 \quad P(i, t2) = \lambda[m(i, t2) - \omega(i, t1)]/ dt \quad (7)$$

233 and

$$234 \quad m(i, t2) = \omega(i, t1)M_{max} / [\omega(i, t1) + [M_{max} - \omega(i, t1)]e^{-\alpha dt}] \quad (8)$$

235 where M_{max} is the asymptotic tumour load and α is the scale parameter of the logistic curve.

236 Parameter estimates from the incremental growth model (λ, α, M_{max}) enabled forward
 237 and backward projection of individual disease burden, which is a Markov process governed
 238 by the disease burden $\omega(i, t-1)$ at the previous time step and the probability density function
 239 over all possible increment values given the growth model (eqn. 6).

240 We used backward projection to estimate the date tumour load was at an assumed minimum
 241 mass of $\omega_{min} = 0.0001$, which we assumed to correspond to an arbitrary initial volume at the
 242 onset of tumour growth (note that we cannot further account for the true underlying
 243 biological process of latent and incubation period and the emergence of first lesions
 244 associated with tumour growth from the given data). We then projected individual tumour
 245 loads $\omega^P(i, t^P)$ according to equations 6-8. Note that the superscript ' P ' is used to indicate

246 projected values rather than likelihood-based estimates from the data. We were not able to
 247 account for individual heterogeneity in growth parameters (λ , α , M_{max}) due to a lack of more
 248 detailed data; in order to realistically project individual disease burdens despite this
 249 shortcoming, we constrained logistic growth of individual tumours such that any projected
 250 value $\omega^P(i, t^P)$ was smaller than any previous data-derived estimate of disease burden and not
 251 larger than any future, data-driven estimate, i.e. $\omega(i, t < t^P) \leq \omega^P(i, t^P) \geq \omega(i, t > t^P)$.

252

253 (4) Force of infection

254 The individual disease state $d(i, t)$ of whether individual i is diseased at time t is another
 255 partially known binary state variable, which is known for all times individuals were captured
 256 and for projected tumour loads but unknown after the last capture for non-diseased
 257 individuals. We modelled $d(i, t)$ based on the infection probability $I(i, t)$, that is the probability
 258 that uninfected individual become infected, conditional they are alive.

259 $I(i, t)$ was modelled with a *logit*-link function as

$$260 \quad \text{logit}[I(i, t)] = \mu_{\Gamma}[\text{age}_{cat}(i, t), \text{period}(t)] + \alpha_{sex}[\text{sex}(i)] + A_{\Gamma} X_{\Gamma}(t) \quad (9).$$

261 Equivalent to the model for $\Phi(i, t)$, we modelled $I(i, t)$ with variation over age classes, sex and
 262 time and used the scaling factor $\delta(t)$ to take unequal time intervals into account; see

263 **Supplementary Information.**

264

265 The model was fitted in a Bayesian framework with Markov Chain Monte Carlo (MCMC)
 266 sampling and the Gibbs Sampler in OpenBUGS 3.2.2 (Lunn *et al.* 2009). Parameter estimates
 267 were calculated as posterior modes and 95% highest posterior density credible intervals (CI)
 268 from 5,000 MCMC samples. Details of model fit and the model code are presented as

269 **Supplementary Information.**

270 We calculated the force of infection $FoI(t)$, that is, the rate at which susceptible individuals
271 acquire DFTD at each time t , as the population average from the infection probability $I(i,t)$.

272 We used the various state and indicator variables described above to calculate
273 summary statistics at the individual (i.e. lifespan, the time until death after the onset of
274 tumour growth or lifetime reproductive output of females) and population level (i.e. disease
275 prevalence, proportion of individuals in different age classes in each capture session).

276 We explored trends and seasonal effects of transmission rates (derived from prevalence
277 estimated from all individuals and, alternatively, mature individuals only) with linear
278 regression models in R (R Development Core Team 2016), running models for each set of
279 MCMC samples to obtain posterior distribution of coefficient estimates.

280

281 RESULTS

282 Strikingly, we found that the overall fitness of host individuals was significantly
283 higher in terms of both survival and reproduction than those of non-host individuals (devils
284 never hosting tumours during their lifetime). The average survival rates of mature (≥ 425
285 days old) non-diseased host individuals was estimated to be 0.7 – 4 times higher than those of
286 mature non-host individuals (odds ratio of 4.7 – 4.9 and CIs 3.3 – 9.0 for β_{host} for the time
287 periods 2006 – 2008 and 2009 – 2011; odds ratio of 1.7 and CI 1.4 – 4.9 for the time period
288 2012 – 2015; temporal differences are only tendencies but not significant because of
289 overlapping credible intervals; **Fig. 2**). Increased tumour loads of diseased host individuals
290 did indeed lead to decreased survival rates, reducing survival of individuals with tumour
291 burdens $> 100 \text{ cm}^3$ to only 9 – 20% of that of non-diseased host individuals with similar
292 effects over time (**Fig. 2**; β_{tumour} , odds ratios of 0.09 – 0.12, CIs: 0.07 – 0.21). Nevertheless,
293 devils with tumours in the smallest size class had higher survival rates than those that never
294 became infected. A larger proportion of host individuals had lifespans between 3 – 4 years

295 compared to non-host individuals, with 56% (CI: 53 – 59%) of hosts surviving to this age
296 compared to only 38% (CI: 34 – 40%) of non-hosts (**Fig. 3**), most having died or dispersed as
297 young before they could get infected.

298 Mature female host individuals reproduced on average 1.3 times (CI: 1.2 – 1.4) in
299 their lifetime, while mature non-host females reproduced on average only 0.7 times (CI: 0.6 –
300 0.9). Moreover, host individuals tended to have larger litter sizes with a 63% (CI: 62 – 64%)
301 chance of a litter sizes of four young opposed to only 47% (CI: 46 – 48%) chance for non-
302 host individuals, which more often had litter sizes of two or three young only.

303 According to our incremental growth model, the average half-life time of tumours
304 (i.e. the progression of individual tumour loads towards half the size of the asymptotic
305 tumour load M_{max}) was 148 days (CI: 114 – 181 days); M_{max} was estimated as 202 cm³ (CI:
306 198 – 223 cm³) and the scale parameter of the logistic growth curve as $\alpha = 0.03$ (CI: 0.028 –
307 0.043, **Fig. S1**). The scale parameter of the Gamma process of incremental growth was $\lambda =$
308 0.8 (CI: 0.6 – 1.4), suggesting that growth of tumour loads was skewed towards relatively
309 small incremental growth, and only occasionally, relatively large increments. Tracking the
310 individual time until death of host individuals after the onset of tumour growth (i.e. a
311 modelled time point prior to the time of first observation), we found that only 11% (CI: 7 –
312 15%) of individuals died within 90 days after the back-projected onset of tumour growth; at
313 least 21% (CI: 13– 29%) of host individuals were likely to survive > 2 years with tumours
314 (**Fig. S2**).

315 Population-level disease prevalence increased from the beginning until mid-term of
316 the study (2006 – 2012), but we found no consistent trend in disease prevalence in the last
317 time period (2013 – 2015) (**Fig. 4**). Disease prevalence and the proportion of non-host
318 individuals did not vary across seasons but exhibited some long-term trends. The proportion

319 of non-host individuals decreased considerably during the first years of the study (2006 –
320 2011) and subsequently increased from 2011 to 2014 (**Fig. 4**).

321 Force of infection was highest in 2012 (posterior mode of 67%, CI 51 – 80%). Despite
322 considerable uncertainty in these estimates as shown by large CIs (**Fig. 5**) we found a
323 significant decrease in the force of infection after 2012 as shown by the odds ratio of the
324 temporal effect (**Fig. S7**). At population level, the number of newly diseased individuals in
325 different capture sessions was positively correlated with the number of diseased individuals
326 in previous capture sessions (Spearman's $r = 0.51$, CI: 0.34 – 0.65) and disease prevalence in
327 previous capture sessions (Spearman's $r = 0.45$, CI: 0.31 – 0.57). Changes in disease
328 prevalence over time were positively correlated with the number of diseased individuals
329 (Spearman's $r = 0.92$, CI: 0.88 – 0.94) and the estimated total mass of all tumour loads at
330 population level (Spearman's $r = 0.72$, CI: 0.28 – 0.89). The force of infection divided by
331 prevalence would estimate the transmission rate β if transmission was frequency-dependent
332 (as previously suggested; McCallum *et al* 2009). There was inconclusive evidence that
333 transmission rate estimates from August 2012 (peak in force of infection) until November
334 2015 declined by approximately 24% (CI: -13 – -29%) during the 3 years of the study with
335 prevalence calculated for all individuals regardless of age, but this trend was not confirmed
336 with prevalence estimates for mature individuals only. There were no clear seasonal
337 differences in transmission rate estimates, which included much uncertainty according to
338 large credible intervals (**Fig. S8**).

339 Declines in the finite population size estimates over time (**Fig. S3**) coincided with
340 declines in the population-level total number of pouch young per year after 2010 (**Fig. S4**).

341 Survival rates differed markedly for different age classes and over time (**Fig. S5**), as did the
342 demographic structure of the populations (**Fig. S6**). Capture rates varied over season with 33
343 – 35% (both CIs: 31 – 39%) capture probability in February/March and November and 27%

344 (both CIs: 24 – 30%) capture probability in May and July/August. Capture probability
345 dropped slightly during the course of the study (**Fig. S7**) and more than doubled for diseased
346 host individuals (γ_{infect}) compared to uninfected individuals.

347 Overall model fit was reasonably good with a Bayesian p-value of 0.52. Model fit of
348 the incremental growth models was less precise with a Bayesian p-value of 0.30; we attribute
349 the lack of better fit largely to the limited data on disease progression and also large
350 individual heterogeneity in tumour growth, for which we could not account in this study with
351 a lack of more detailed field data. Results on the variation in survival rates for different age
352 classes, population size estimates, and the age composition in each capture session are
353 presented as **Supplementary Information**.

354

355 **DISCUSSION**

356 We found an unexpected and novel result - devil facial tumour disease (DFTD), a
357 transmissible and devastating cancer, selectively impacts the otherwise most fit individuals in
358 the population. Despite being affected by disease, host individuals (those that eventually
359 become infected) had both higher survival and greater reproductive output than non-host
360 individuals, in terms of both more annual breeding attempts and larger litter sizes. This
361 challenges the conventional wisdom that infectious disease differentially affects *less fit*
362 individuals in a population (de Castro & Bolker 2005). We emphasize that the novel insights
363 in terms of individual fitness in relation to disease status gained in this study were only
364 possible by analysing disease progression, survival and reproduction in an integrative model
365 framework that accounts for the most likely disease states of individuals throughout their
366 lifetimes.

367 Our finding that devils with relatively high fitness are also those most likely to
368 become infected suggests that it is the socially dominant animals that are at highest risk of

369 infection and death from DFTD. These are the individuals that are likely to survive longer
370 than the less fit mature individuals in the population, which most likely die from other causes
371 before they are able to reproduce. This result is consistent with the finding of a previous
372 study showing the most frequent biters (i.e., socially dominant animals) are most likely to
373 become infected (Hamede *et al.* 2013). If infection selectively removes dominant individuals
374 from a population, there may be important long-term consequences for the social structure
375 and viability of the population, as well as for disease transmission. For example, culling of
376 European badgers (*Meles meles*) disrupts social organisation and leads to increased
377 movement of badgers and disease transmission to cattle (Donnelly *et al.* 2006). Likewise,
378 selective animal removal through harvesting can change the demographic structure and
379 population growth of many species (Milner *et al.* 2007).

380 Our results also have implications for understanding how disease-induced
381 evolution in Tasmanian devil populations may be occurring. In particular, our model
382 framework provides the opportunity to explore whether devils may evolve resistance to
383 infection or rather tolerance to the impacts of infection, both being important host adaptation
384 strategies (Råberg *et al.* 2009). Several lines of evidence provide robust support for the
385 assertion that infected devils are under strong selective pressure. First, high mortality of
386 adults from DFTD leads to rapid population declines (McCallum *et al.* 2009). A recent study
387 provided evidence of substantial changes in the frequency of genes associated with immune
388 function in devil populations that have been infected for as little as eight years (Epstein *et al.*
389 2016). Third, a small number of individuals are able to mount an immune response and, in
390 some, tumours regress (Pye *et al.* 2016). In this context, the implications of our novel results,
391 that it is that the otherwise most fit devils become infected, are intriguing. If adult devils with
392 high fitness are those that become infected, the potential for selection for resistant animals
393 would be limited. However, our results also demonstrate a recent decline in the force of

394 infection and transmission rate. This leads to the question of whether devils in this population
395 may have developed resistance to infection. The initial increase in the force of infection from
396 2006 to 2012 (see Figure 5) is to be expected as the tumour increased in prevalence within
397 the host population after disease emergence. It may also be a result of the replacement of a
398 tetraploid tumour karyotype with a diploid karyotype which took effect from 2011 onwards
399 (Hamede *et al.* 2015). The recent decline in the force of infection and transmission rate
400 warrants further investigation, and could be due to a number of factors. There is evidence of
401 selection at West Pencil Pine in chromosomal regions containing genes related to immune
402 and cancer function (Epstein *et al.* 2016), possibly indicating evolution of resistance, as well
403 as evidence of immune responses to DFTD resulting in tumour regressions and recovery after
404 infection (Pye *et al.* 2016). Individual heterogeneity in devil behaviour such as physical
405 interaction and biting is another possibility. The recent decline of the force of infection could
406 have resulted from a reduction in the number of socially dominant devils from the population,
407 if these are responsible for most transmission events. Group living and mating strategies can
408 shape social contact networks among individuals that mediate parasite exchange (Liljeros *et*
409 *al.* 2003; Cauchemez *et al.* 2011) and disease risk (Altizer *et al.* 2003; Drewe 2010; Kappeler
410 *et al.* 2015). The possibility of synergistic effects between co-evolutionary dynamics of host-
411 pathogen interactions and disease-driven changes in social structure over time necessitates
412 caution when interpreting changes in disease transmission in context of host defence
413 mechanisms. For future studies, it will be desirable to refine estimates of disease transmission
414 rates that are currently blurred by large uncertainty and cannot account for individual
415 heterogeneity in social status and behaviour due to the lack of data.

416 Disease tolerance might manifest in a number of ways, but one would be longer
417 survival when carrying a tumour burden of a given size. Figure 2 shows no evidence that this
418 has occurred, with the relationship between tumour size and mortality rate being

419 indistinguishable in the three time periods. A confounding factor, however, is the change in
420 the dominant tumour karyotype in the population from tetraploid in the early stages of the
421 epidemic to diploid karyotype during the course of the study (Hamede *et al.* 2015).
422 Unfortunately, distinguishing diploid from tetraploid karyotypes was not possible for most of
423 the individuals analyzed herein, and this information was therefore not included in our study.
424 Moreover, recent molecular evidence of a protective immune response of devils against
425 DFTD recorded from our study site (Pye *et al.* 2016) suggests that immune responses might
426 impact disease tolerance through regression of tumours. Reconciling these facts with our
427 findings of how population-level disease dynamics may change over time requires further
428 analysis of how individual-level heterogeneity in host and tumour genotypes and the
429 behaviour of adult 'hosts' and 'non-hosts' drive variation in demographic rates and infection
430 risk and how this translates into population-level pattern in disease dynamics.

431 Our estimates of the time until death following infection are longer than the 6
432 months previously reported (McCallum *et al.* 2009; Ujvari *et al.* 2016). These previous
433 estimates were for time until death after first detection of tumours. Estimation of the
434 incubation period and its frequency distribution is a challenging problem for DFTD
435 (McCallum *et al.* 2009). Our new, model-based estimation of survival time includes back-
436 projection of growth to a very small initial tumour volume. This may not estimate the actual
437 incubation period fully, but is a substantial improvement over previous approaches, which
438 have relied on anecdotal information on the appearance of tumours in captive animals which
439 had not been exposed to infection for extended periods (Pycroft *et al.* 2007).

440 To determine whether and how disease-induced evolution within the devil
441 population and reciprocal evolution within the tumour population is occurring requires
442 further data and modelling. The modelling and analytical framework, we have presented in

443 this paper provides a template for performing such analysis, which should be also applicable
444 to a wide range of other emerging infectious diseases in natural populations.

445

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460

461 **Authorship:** The project was initialized by MEJ, RKH and HIM, and RKH collected data;
462 KW conceived and performed the analysis and wrote the first draft of the manuscript. All
463 authors interpreted results and contributed to revisions.

464

465 **Data accessibility statement:** If the manuscript is accepted for publication in Ecology
466 Letters, the data supporting the results will be archived in an appropriate public repository
467 such as Dryad or Figshare and the data DOI will be included at the end of the article.

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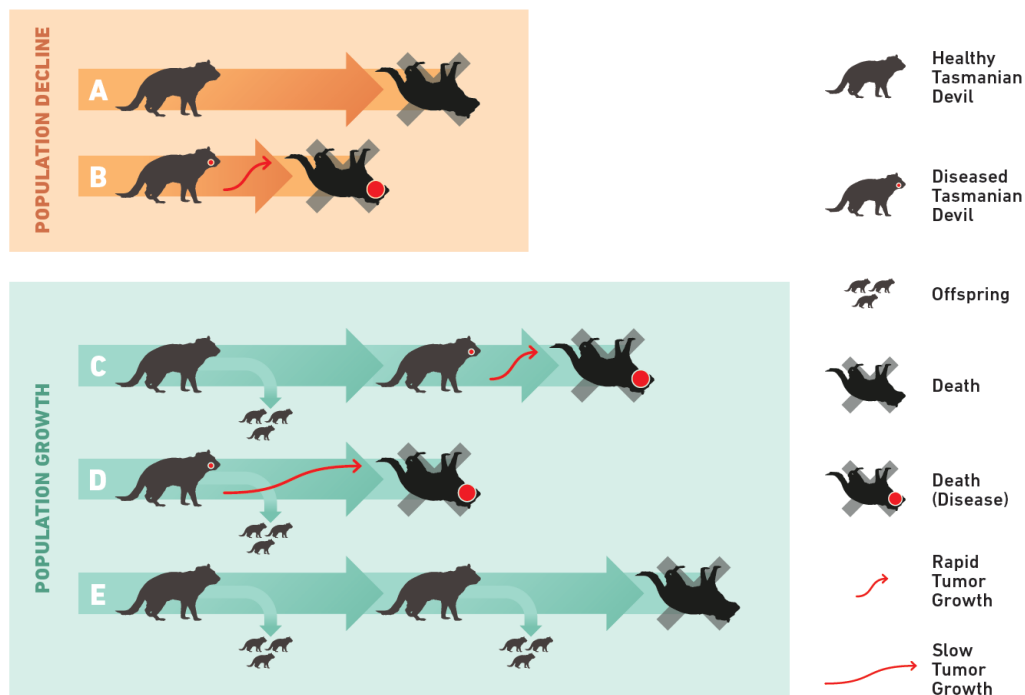
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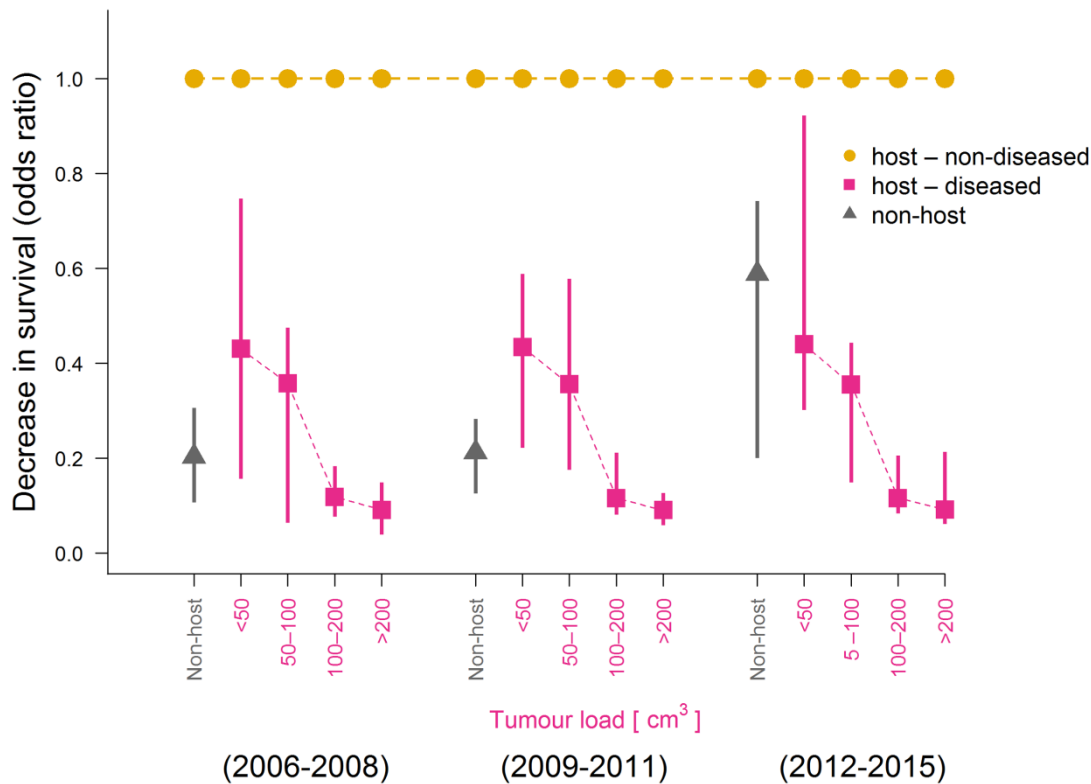


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593 **Figure 1.** Illustration of possible synergistic effects of host survival and fecundity on long-
 594 term population growth in context of disease onset and progression such as increasing tumour
 595 load on Tasmanian devils. Horizontal thick lines indicate individual devil survival over time,
 596 small devils reproduction and red dots infestation with tumours. Devils may not reproduce
 597 because of their physical condition or social status independent of the disease (A), or, because
 598 of a highly fatal disease with rapid progression and death (B), promoting population decline.
 599 However, host individuals can contribute to the reproductive pool and population growth if
 600 they are diseased late in life (C), or, if slow disease progression allows reproduction of
 601 diseased host individuals (D). Healthy non-host individuals may reproduce several times in
 602 their life (E). The outcome of these strongly coupled demographic and epidemiological
 603 interactions can only be understood if analysed in a consistent framework.

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607 **Figure 2.** Estimated decrease in survival rates for mature non-host individuals (i.e. those that
 608 never become infected; grey triangles) and host individuals with certain tumour loads (red
 609 squares) compared to non-diseased host individuals (i.e. prospective host individuals prior to
 610 the onset of tumour growth). Triangles and squares are posterior modes of the odds ratios of
 611 the survival rates compared to those of non-diseased host individuals (baseline value at 1,
 612 shown in orange), vertical bars are 95% credible intervals.

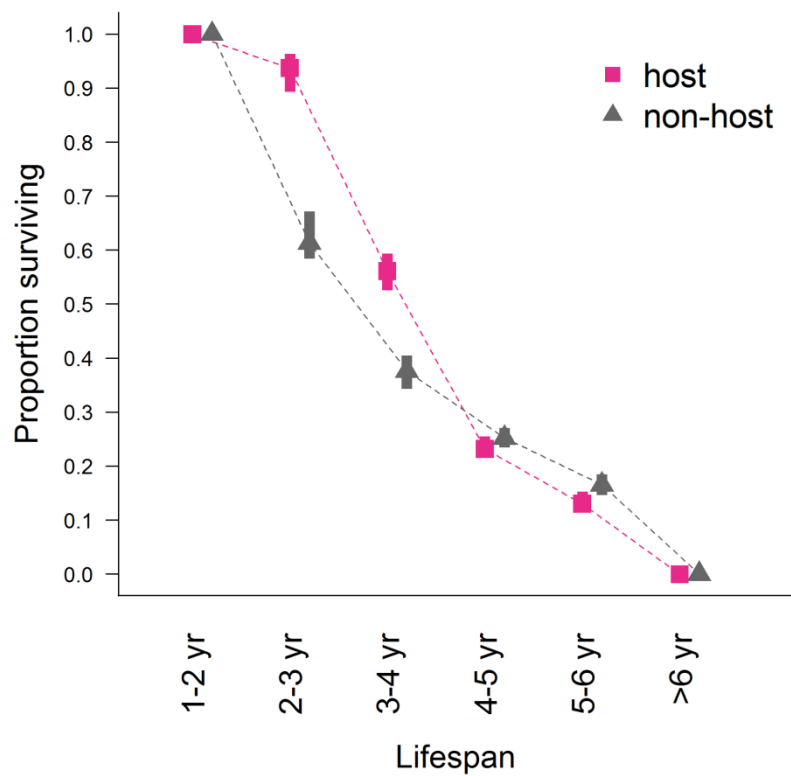
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619 **Figure 3.** Proportion of Tasmanian devil individuals with different lifespan estimates based
 620 on their classifications into host (harbour tumours at any stage during their lifetime) and non-
 621 host (no tumours observed) individuals. Symbols represent the posterior mode estimates of
 622 the proportion of individuals in each class of expected lifespans (1–2, 2–3, 3–4, 4–5, 5–6, > 6
 623 years). Vertical bars represent 95% credible intervals based on the uncertainty in individual
 624 lifespan estimates from the state-space model.

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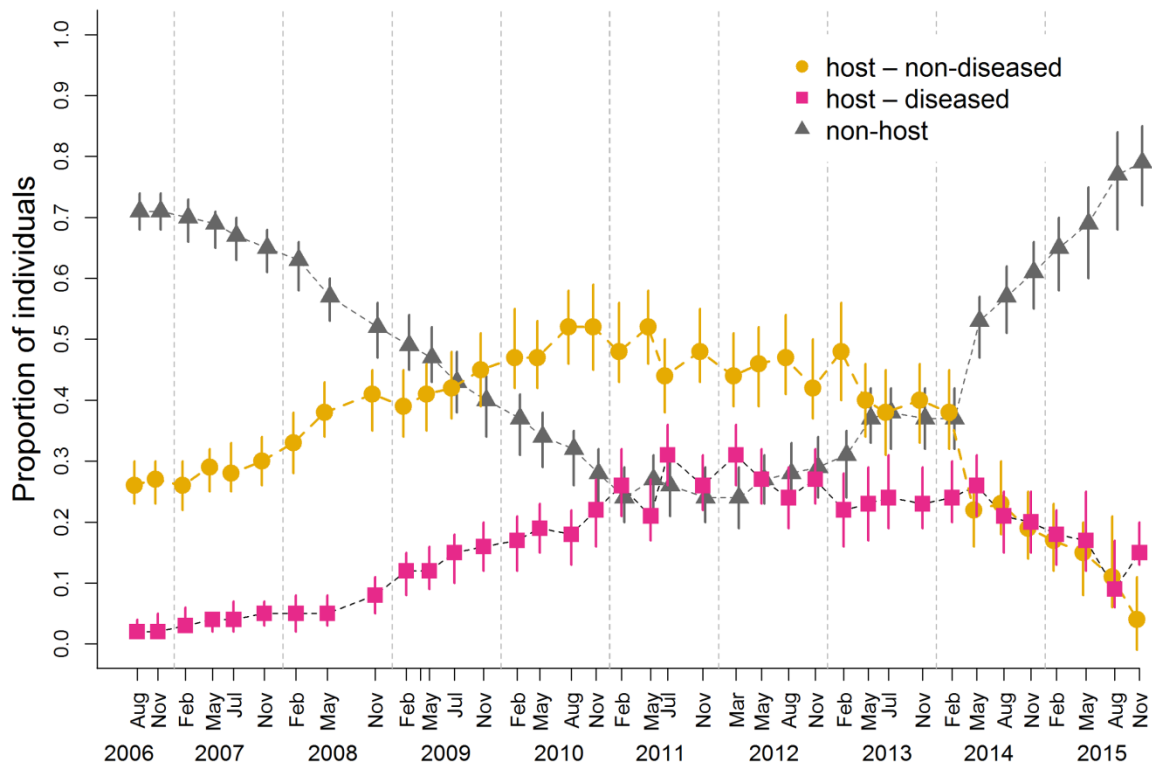
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632 **Figure 4.** Changes in the proportion of individuals with different health status for devil facial
 633 tumour disease over 10 years. Disease prevalence, that is the proportion of individuals that
 634 are hosts *and* are diseased are plotted with pink circles/bars. Individuals without tumours are
 635 denoted as ‘host – non-diseased’ (orange circles/bars) if they were expected to acquire
 636 tumours later in their life and as ‘non-host’ (grey triangles/bars) if they never hosted tumours.
 637 Symbols are posterior mode estimates, bars present 95% credible intervals. For each time
 638 step, the proportions of individuals in the three different states sum to one.

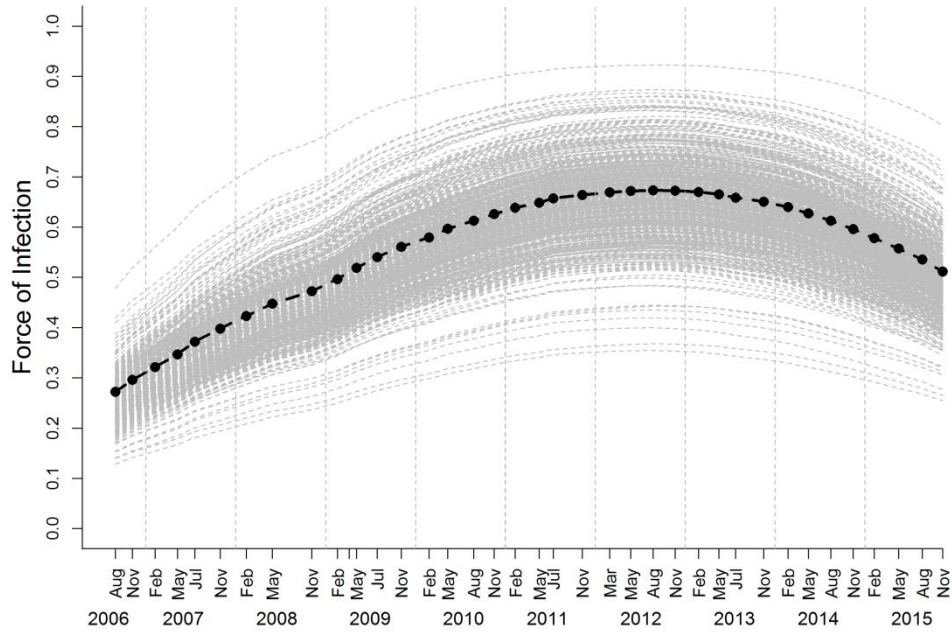
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645 **Figure 5.** Estimated force of infection (rate at which susceptible individuals become diseased
 646 per year) for devil facial tumour disease over 10 years. Black dots are posterior mode
 647 estimates, bars present 95% credible intervals from sampling possible disease progression at
 648 individual level.