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Multi-state modelling reveals sex-dependent transmission, progression and severity of tuberculosis in wild badgers

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SUMMARY

Statistical models of epidemiology in wildlife populations usually consider diseased individuals as a single class, despite knowledge that infections progress through states of severity. Bovine tuberculosis (bTB) is a serious zoonotic disease threatening the UK livestock industry, but we have limited understanding of key epidemiological processes in its wildlife reservoirs. We estimated differential survival, force of infection and progression in disease states in a population of Eurasian badgers (*Meles meles*), naturally infected with bTB. Our state-dependent models overturn prevailing categorizations of badger disease states, and find novel evidence for early onset of disease-induced mortality in male but not female badgers. Males also have higher risk of infection and more rapid disease progression which, coupled with state-dependent increases in mortality, could promote sex biases in the risk of transmission to cattle. Our results reveal hidden complexities in wildlife disease epidemiology, with implications for the management of TB and other zoonotic diseases.

Key words: Bovine tuberculosis, European badger, state-dependent modelling, survival, wildlife disease.

INTRODUCTION

Many of the world's important diseases of humans and livestock are zoonotic, being harboured by and transmitted from wildlife reservoirs [1]. Management of these diseases requires detailed understanding not just of their clinical epidemiology, but also the demographic processes of disease transmission, and of progression and disease-induced mortality, which may themselves vary in disease states, sexes or ages of hosts. Disease progression is commonly estimated and modelled in human epidemiological studies (e.g. [2, 3]). Few models of wildlife epidemiology consider disease states beyond the standard susceptible-infected-recovered/susceptible-exposed-infected-recovered (SIR/SEIR) categories of classical models and we are

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not aware of any capture–mark–recapture (CMR) multistate analysis that directly addresses parameterization of disease progression through intermediate disease states in wildlife populations. Predictions of effective disease management strategies, based on mathematical models, tend to be highly sensitive to transmission, progression and mortality parameters [4–7]. Therefore, better understanding of state-dependent epidemiology should improve management strategies, providing benefits to human wellbeing or the economic viability and health and welfare standards of livestock farming. Here we use state-dependent statistical models to reveal complexities in the ecological epidemiology of an important zoonotic disease: bovine tuberculosis in wild badgers.

Bovine tuberculosis (TB caused by *Mycobacterium bovis*) has severe consequences for the livestock industry in the UK. TB prevalence in cattle has increased in recent decades [8, 9], with substantial costs for farmers and other taxpayers. Badgers are a wildlife reservoir of TB in the UK and the Republic of Ireland and are strongly implicated in the transmission of *M. bovis* to cattle [10, 11]. In addition to cattle control measures, badger culling has been used intermittently as a disease control option in the UK and Republic of Ireland [12]. Additional strategies include enhanced biosecurity measures and vaccination [13, 14].

Over the past 25 years, several models have been used to simulate the dynamics of TB in badger populations. In early SEI models [4, 15], badgers were considered to become infectious upon detection of *M. bovis* bacilli excreted from lesions. Estimates of disease-induced mortality in infectious badgers ranged from 0% [15] to 100% [4]. Another long-standing categorization of badgers divides the infectious category into 'excretors' (badgers that are found to shed TB bacilli intermittently) and 'super-excretors' which are assumed to be more consistently infectious [5, 6]. Super-excreting badgers have been modelled as experiencing enhanced disease-induced mortality ranging between 22·4–60% [6, 16]. Parameter estimates of transmission, disease progression and disease-induced mortality are prerequisites for the prediction of TB prevalence in host populations [4, 5]. These parameters are drivers of disease incidence in the established badger–TB model [17] and rank among the key determinants of the rate of cattle herd incidence. Therefore, uncertainty in their magnitude and complexity needs to be reduced. A key question is whether the categorization of TB infection in badgers, according to stages based on diagnostic test outcomes, reflects biologically relevant and discernible categories of host survival and disease progression.

Detecting population-level impacts of pathogens requires long-term studies of the host and infective agent in their natural environment. At Woodchester Park, Gloucestershire, UK, a population of naturally TB-infected badgers have been studied since 1976 [18]. Two main diagnostic approaches have allowed assessment of the TB status of each badger over most of this period. The Brock ELISA (enzyme-linked immunosorbant assay [19]) test detects *M. bovis* antibodies in blood serum. The second diagnostic test cultures *M. bovis* from sputum, faeces, urine, or swabs of wounds and abscesses [20]. Although a relatively insensitive diagnostic approach [21], positive culture gives an unequivocal indication of active excretion of *M. bovis* and hence an infectious state.

Only one previous study has attempted to parameterize badger mortality using demographic data from Woodchester Park [22]. These authors classified badgers as uninfected, Brock ELISA positive, single culture positive, and super-excreting. However, the definition of a super-excretor was a badger with more than one culture-positive result, from any sample. The inherent weakness in this approach is that it classified an animal which was excreting only intermittently from the same source, as a super-excretor, even if the disease had not progressed. As no alternative categorizations were considered these authors may have overlooked disease states of intermediate severity. In other host species, TB infection exhibits a wide spectrum of pathology [23, 24] and so exploration of disease-state-specific mortality is likely to be productive in the badger–TB system. As TB infection in badgers progresses, the number of sites of excretion increases [25, 26], hence the existence of multiple excretion sources seems an obvious candidate proxy for disease severity.

Here we use state-dependent statistical modelling of the CMR histories of a marked population of wild badgers to assess sources of variation in class-specific epidemiological parameters, focusing on survival and disease progression (transition between disease states). We present a new classification of badgers based on disease severity, and provide estimates of mortality, force of infection and rate of disease progression. Our analyses improve upon previous estimates of TB-induced mortality in badgers, and more significantly will allow better evaluation of management strategies and improve our understanding of the

outcomes of generalized or targeted management approaches to wildlife disease.

METHODS

Recapture Data

We used live capture data collected at Woodchester Park from 1984 to 2005 inclusive, as this period used consistent protocols consisting of quarterly trapping events at each social group's sett. Trapped badgers were anaesthetized and tattooed with an individual ID upon first capture. At every capture event the location, sex and age group were recorded (for detailed methods see [27]). Blood samples were tested for antibodies to *M. bovis* using the Brock ELISA test [19]. Samples of faeces, urine, sputum and pus from abscesses and/or bite wounds were taken for culture of *M. bovis* [20].

Capture histories of 88 encounters (22 years × 4 trapping periods/year) were created for each badger. We considered a badger to be in one of four states on each encounter, classified according to the results of the diagnostic tests. A badger with no positive ELISA results and no positive culture results was classed as 'test negative' (N), while a positive ELISA test result without positive culture was classified as 'ELISA positive' (P). Accurate diagnosis of TB in live badgers is difficult due to limitations in the performance of the diagnostic tests [28]. To control for a specificity of 89–94% [28, 29] of the ELISA test we considered badgers with only one ELISA-positive result, followed by entirely negative results thereafter, to be false positives [30], reducing the likelihood of misdiagnosis of infection. A positive culture result from a sample from one body site resulted in classification as a 'one-site excretor' (X) and if bacteria were isolated from more than one body site then the animal was classified as a 'multi-site excretor' (XX). These categories (Fig. 1*a*) recognize that the number of excretory sites increases as TB infection progresses in badgers, indicating the spread of lesions or an increase in their severity [25, 26]. Models were also run using the standard definitions of 'test negative', 'ELISA positive', 'excretor' and 'super-excretor' [22], to compare model fit with our proposed categorization. The key difference is that the prevailing 'super-excretor' badger has multiple positive culture samples inclusive of culture positives from the same site, while our 'multi-site excretor' badger only includes multiple positives from different body sites. Additionally, to evaluate whether inclusion of multiple disease states provides important information, we compared standard susceptible-infected (SI) models with our proposed categorization.

State-dependent statistical modelling framework

Data were analysed using multi-state models in the program MARK [31] via the R interface [32] and the package RMark [33]. Multi-state models [34] were used to analyse time-, age group (cub and adult)-, sex- and disease-state-specific variation in quarterly rates of survival, recapture and transition between disease states. We compared the performance of state-dependent models that included the established and the novel classifications of disease state. Models were assessed using Akaike's Information Criteria (AIC) adjusted for overdispersion (QAIC) [35]. 'Better' candidate models were indicated by lower AIC values. Substantial support for the best model alone is indicated when rival models all have QAIC >2 units larger [35]. We tested for overdispersion of models using the 'median c-hat' method as implemented in the program MARK [31]. We applied the highest estimate of overdispersion (1·28) to the results, which did not qualitatively change the findings but means that the significance of differences between parameter estimates is conservative. Significant differences in survival estimates of male and female badgers in different disease states were tested using Z scores with false discovery rate adjustment for multiple testing. Adjusted P values $<0{\cdot}05$ were considered significant.

RESULTS

During the period 1984–2005, 1640 badgers were trapped (674 males, 786 females). These individuals contributed 7699 capture events comprising 6739 uninfected occasions, 515 ELISA positive occasions, 285 one-site excretor occasions and 160 multi-site excretor occasions.

Best models

The best models indicated that survival (Φ) probabilities varied according to sex and disease status (Table 1). There was no evidence of age-specific mortality (Table 1). Recapture probabilities varied considerably over the 22-year period with apparent seasonality. Males had a consistently higher probability of recapture than females throughout all

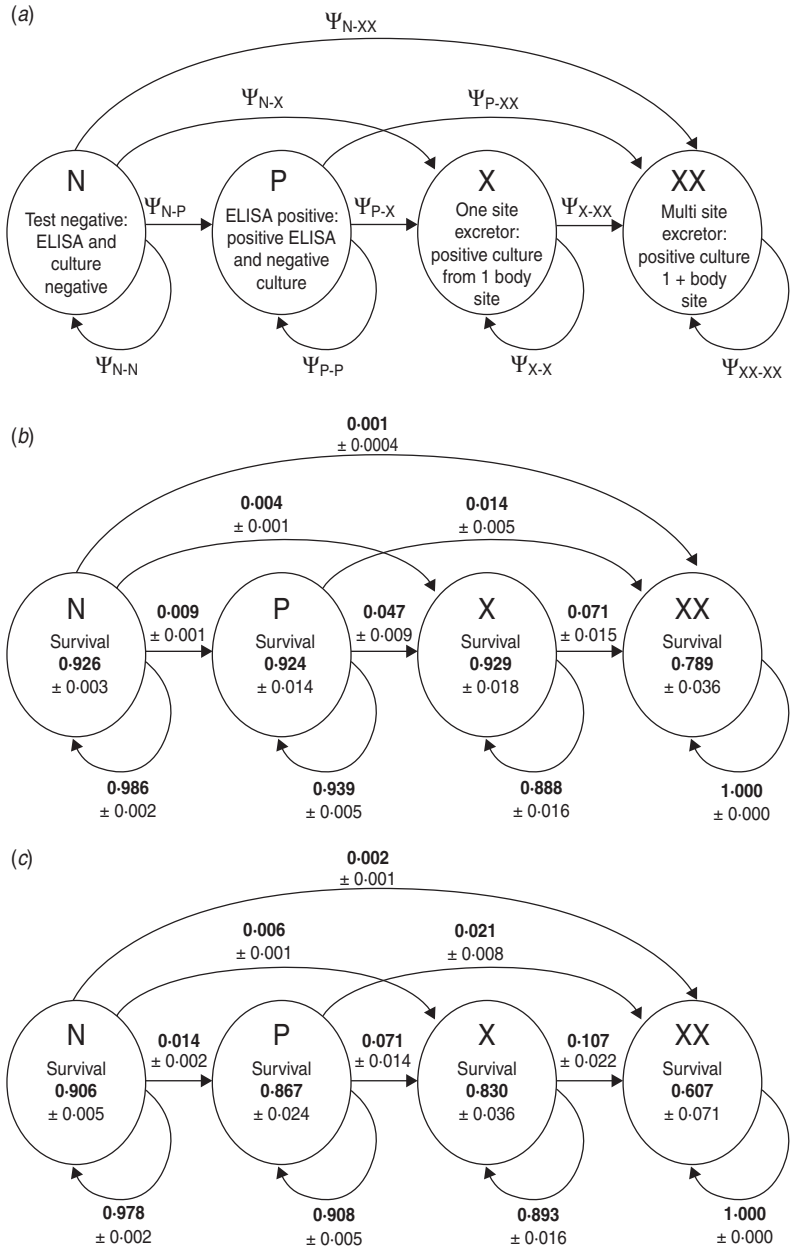

Fig. 1. (*a*) Depiction of the multi-state model used for analyses. Transitions could only occur in the direction of the arrows. Quarterly estimates of state-transition rates and their standard errors for (*b*) female and (*c*) male badgers are provided, for surviving individuals.

trapping sessions. Quarterly recaptures (±standard error) varied from 0·15±0·03 to 0·73±0·03 for females and 0·20±0·03 to 0·78±0·03 for males. Transition (Ψ) probabilities in states depended on sex and disease status (Table 1), but not age or time. The new categorization of disease states improved model fit markedly compared to the previous categorizations of uninfected, ELISA positive, excretor and super-excretor [22] (Table 1). There was also more support for the inclusion of multiple disease states (N, P, X, XX) than the standard, binary SI epidemiological models (Table 1).

Survival

The severity of TB, as indicated by diagnostic test results, influenced quarterly survival probabilities in badgers. After adjustment for multiple comparisons, for both males and females the lowest survival probability occurred in multi-site excretors (Figs. 1*b*, *c*, 2).

Table 1. *Candidate multi-state models of badgers categorized by disease state*

Survival	Transition	Recapture	QAIC	Number parameters	QAIC weight	Model likelihood
New categorization						
Disease × sex	**Disease + sex**	**Time + sex**	**20143·25**	**103**	**0·742**	**1**
Disease + sex	**Disease + sex**	**Time + sex**	**20145·37**	**100**	**0·257**	**0·35**
Disease × sex × age	Disease + sex	Time + sex	20957·96	111	0	0
Age × sex	Disease + sex	Time + sex	20181·86	99	0	0
Sex + age	Disease + sex	Time + sex	20179·91	98	0	0
Prior categorization						
Disease × sex	Disease + sex	Time + sex	20624·15	109	0	0
Uninfected/infected (SI) categorization						
Disease × sex	Disease + sex	Time + sex	20166·88	99	0·00001	0

QAIC, Akaike's Information Criteria adjusted for overdispersion.
Columns 1–3 describe the additive (+) or interactive (×) effects of sex, age and disease state on survival, transition and recapture probabilities. The 'best' two models (shown in bold) classified badgers as negative (N), ELISA positive (P), one-site excretor (X) and multi-site excretor (XX). Competing models included: previous infectivity categorization of uninfected, ELISA positive, excretor and super excretor; simplified categorization of uninfected and infected; inclusion of age effects. Competing candidate models had zero model likelihood therefore only relevant examples are provided.

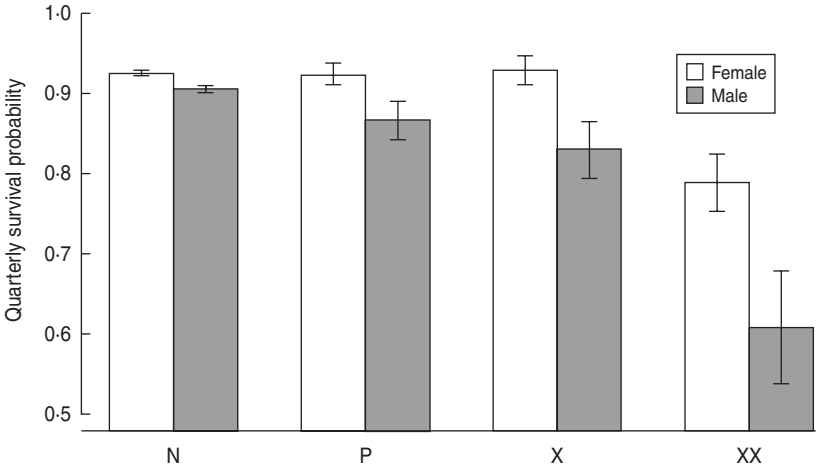

Fig. 2. Quarterly survival estimates of female and male badgers when classified as: negative (N), ELISA positive (P), one-site excretor (X) and multi-site excretor (XX). In each case the parameter estimate is shown ± standard error.

Quarterly survival probabilities of males in every infected state were significantly lower compared to uninfected male badgers (90·6% survival probability) and decreased from ELISA positive (86·7%, $Z=-1{\cdot}81$, $P=0{\cdot}035$), to one-site excretor (83%, $Z=-2{\cdot}59$, $P=0{\cdot}005$) and finally to multi-site excretor (60·7%, $Z=-6{\cdot}06$, $P<0{\cdot}001$). Female survival probability did not vary in uninfected and initial stages of disease progression (uninfected 92·6%, ELISA positive 92·4%, one-site excretor 92·8%), but a significant decrease in survival was observed between uninfected badgers (92·6%) and multi-site excretors (78·9%, $Z=-5{\cdot}36$, $P<0{\cdot}001$).

Male badgers had significantly lower survival probability than females across all states (Fig. 2): uninfected state ($Z=-2{\cdot}54$, $P=0{\cdot}005$), ELISA-positive state ($Z=-2{\cdot}14$, $P=0{\cdot}016$), one-site excretor state ($Z=-2{\cdot}63$, $P=0{\cdot}004$) and multi-site excretor state ($Z=-2{\cdot}377$, $P=0{\cdot}034$).

These results correspond to the following annual survival estimates, exclusive of cub-adult age groups, for males (uninfected 67·4%, ELISA positive 56·5%, one-site excretor 47·5%, multi-site excretor 13·4%), and females (uninfected 73·5%, ELISA positive 72·9%, one-site excretor 74·2%, multi-site excretor 38·7%).

Transition between disease states

Transition rates from multi-state models provide a measure of the probability of an individual becoming infected and also of the disease progressing. The best supported models in the candidate set showed that transitions depended on the sex and disease state of the individual badger (Table 1).

The force of infection, i.e. the probability of moving from an uninfected to an infected state, was higher for males than females (Fig. 1*b*, *c*). Hence, 2·2% of males became infected in any quarterly period compared to 1·4% of females. Males had a higher probability of disease progression than females: 7·1% of ELISA-positive males progressed to be detected as a one-site excretor in a quarterly period compared to 4·7% of females. Males were also more likely to become multi-site excretors with 10·7% of males in the one-site excretor category progressing to this stage quarterly, compared to just 7·1% of females (Fig. 1*b*, *c*).

DISCUSSION

Studies of the epidemiology of zoonotic diseases have traditionally viewed the wildlife reservoir as a homogeneous population, with limited appreciation of variation in transmission, progression and mortality in demographic classes or disease states. In systems where stage-specific demographic information is available, state-dependent statistical modelling can reveal epidemiological complexities that could in turn be key drivers of disease persistence, and transmission between wildlife hosts and livestock or humans. Better understanding of these complexities should influence the assessment of disease management strategies. The badger–TB interaction exemplifies this argument: we have shown that key epidemiological parameters, to which current predictions of management options are highly sensitive [17], vary among disease states, and are sex-specific but not age-specific. These parameters will be incorporated into future TB models for improved evaluation of management strategies.

Male badgers suffer increased mortality during intermediate stages of disease progression, while females do not. Incorporating disease states of varying severity uncovered this additional variation and provides a better explanation of survival than a more traditional SI approach. We have confirmed [18, 22] that survival rates of uninfected male badgers are lower than in females. We have also confirmed that survival rates of both sexes are significantly lower in multi-site excretors than in uninfected badgers [22], and shown that multi-site excretor males suffered 29·9% additional mortality per quarter, double the additional mortality seen in females in the same state. Our results challenge the prevailing wisdom that cub survival rates are lower than those of adults [4], although mark–recapture data cannot inform on mortality of offspring prior to emergence from natal setts.

This is the first study to provide empirical estimates of the force of infection, and rate of progression, of TB in badgers. Males were more likely to become test positive, suggesting that males are more liable to acquire infection. Further work is required to determine whether this force of infection is density- or frequency-dependent, *sensu* the transmission parameters of classic epidemiological models [36]. We also found that males progress through disease states more rapidly than females. Both behavioural and immunological mechanisms may cause the observation of higher infection risk and faster disease progression in male badgers. Males tend to range further than females [37], perhaps increasing their risk of exposure to sources of TB. Males are more territorial [37]: associated incidence of bite wounds exposes them to a different route of infection compared to females, resulting in different patterns of disease progression [38]. Alternatively males may have weaker, or compromised, immune responses, which would increase all three epidemiological parameters. Teasing apart behavioural and immunological mechanisms will require detailed assay of infection and disease progression in individual badgers, and the answer could determine the efficacy of the various TB management strategies for badgers. It remains unclear whether males or females are most responsible for transmission of TB to other badgers or to cattle: males progress to infectious states more rapidly but are more likely to die; females spend more time in infectious states and might transmit infection to offspring; males might cause more transmission due to their wider-ranging movement. A complete demographic consideration of TB epidemiology will require us to model state-dependent fecundity, recruitment and dispersal parameters.

Current tactical models that help inform UK policy related to bovine TB control have found that both disease prevalence and cattle herd breakdown rates are sensitive to badger TB transmission rates, mortality rates and disease progression [17]. Our study

contributes a significant revision of these key parameters, and yields novel demographic insight into the sex- and state-dependent epidemiology of TB in a wildlife reservoir. We recommend the use of this revised disease categorization, and improved epidemiological parameters, to increase the predictive power of strategic models for control of bovine TB. Disease-transmission and disease-induced mortality are critical parameters in any infectious disease model, therefore we recommend multi-state modelling for the study of the ecological epidemiology of wildlife reservoirs of any diseases that transmit to humans or livestock.

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DECLARATION OF INTEREST

None.

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