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Analysis of Lifetime Mortality Trajectories in Wildlife Disease Research: BaSTA and Beyond

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Abstract: Wildlife hosts are important reservoirs of a wide range of human and livestock infections worldwide, and in some instances, wildlife populations are threatened by disease. Yet wildlife diseases are difficult to monitor, and we often lack an understanding of basic epidemiological parameters that might inform disease management and the design of targeted interventions. The impacts of disease on host survival are generally associated with age, yet traditional epidemiological models tend to use simplistic categories of host age. Mortality trajectory analysis provides the opportunity to understand age-specific impacts of disease and uncover epidemiological patterns across complete life histories. Here, we use Bayesian survival trajectory analysis (BaSTA) software to analyse capture-mark-recapture data from a population of wild badgers *Meles meles* naturally infected with *Mycobacterium bovis*, the causative agent of tuberculosis in badgers and cattle. We reveal non-constant mortality trajectories, and show that infection exaggerates an age-dependent increase in late-life mortality. This study provides evidence for actuarial senescence in badgers, a species previously believed to display constant mortality throughout life. Our case study demonstrates the application of mortality trajectory analysis in wildlife disease research, but also highlights important limitations. We recommend BaSTA for mortality trajectory analysis in epidemiological research, but also suggest combining approaches that can include diagnostic uncertainty and the movement of hosts between disease states as they age. We recommend future combinations of multi-state and multi-event modelling frameworks for complex systems incorporating age-varying disease states.

Keywords: Bayesian survival trajectory analysis; survival; mortality; Bayesian inference; senescence; population dynamics

1. Introduction

Investigating the epidemiology of any disease in wild populations is challenging because of the practical difficulties in monitoring both infections and their wild hosts [1], yet wild animals are important contributors to many emergent and widespread infections of humans and livestock worldwide [2]. Consequently, any improvements in our understanding of wildlife disease epidemiology can be beneficial to human health, animal welfare and productivity, as well as to biodiversity conservation [1,3]. Disease-related mortality is a critical parameter in any epidemiological model [4] and methods for its estimation, developed for the study of human populations, are now commonly used in studies of

wildlife [5]. Disease can increase rates of host mortality [6,7] and, in extreme cases, can contribute to decline and risks of species extinction [8,9]. Disease-induced mortality is commonly modelled as a simple increase in otherwise fixed mortality rates at particular life stages [10,11] but the reality can be much more complex. Mortality trajectories reveal patterns in age-specific mortality that are often missed when using fixed rates in discrete age classes, yet the inclusion of these trajectories in epidemiological models is rare. The ability to accurately model factors that influence mortality is fundamental to any demographic investigation and the inclusion of mortality trajectories could offer greater precision whilst uncovering subtle variations in the patterns of age-specific mortality. Here we show that the inclusion of disease status, alongside full mortality trajectory analysis, can reveal disease-induced changes in the shape of lifetime schedules of mortality.

Predicted increases in the proportion of the global human population living over the age of 80 [12] have attracted substantial economic investment and scientific interest [13] in age-associated diseases in humans. Disease effects have been shown to vary with age in both human [14] and now non-human animals [15]. While such variation can have a direct impact on population size [16], empirical studies of age-specific causes of mortality in wild populations are scarce [17]. The decline of physiological function with age, i.e. senescence, can affect fecundity [18], morphological traits [19], behaviour [20], and physiology [21] but most commonly it refers to an increase in the rate of mortality with age, known as actuarial senescence [22]. A long-standing belief that environmental factors would result in an animal's death long before the impact of senescence became manifest has now been shown to be false [23]. The emergence of several high-quality, long-term demographic studies, combined with theoretical and statistical advances, have since revealed senescence in many wild populations of various species, and have promoted the study of factors affecting senescence in the wild. Traditional approaches in wildlife epidemiology have focused on estimating fixed mortality parameters for a finite and predetermined number of age categories (e.g., cubs versus adults [24]), which results in the loss of information and risks unnecessarily coarse conclusions. Mortality trajectory analysis, which considers rates of mortality through the entire lifespan, is a means of mitigating some of these problems, but until recently has been difficult to employ with wildlife populations. This is because of several statistical challenges [25], as well as the requirement to monitor marked individuals through entire life histories [23]. Furthermore, the accurate interpretation of mortality trajectories and their associated parameters requires ecological understanding of a species' behaviour and life strategies [26], as well as suitable model selection through comparisons of model fit [27]. If an inappropriate model is fitted to the data, then subsequent conclusions are often specious.

Several mathematical functions have been used to describe lifetime trajectories of age-specific mortality. Historically, the preferred choice was the Gompertz curve [28], which describes mortality as increasing exponentially with age from an intercept representative of an initial baseline risk of death. The more flexible Weibull distribution [29] has recently been used in survivorship analysis, and can accommodate accelerating increase, decelerating increase, decreasing, and constant mortality [30], but can fail to capture early decelerations in mortality rates. Makeham [31] proposed that death could be separated into age-dependent and age-independent sources, resulting in the addition of a "Makeham" term (a constant) to established mortality functions (e.g., Gompertz–Makeham, Weibull–Makeham, etc.). Criticism of these models has focused on the omission of individual heterogeneity, leading to potentially flawed statistical inference [32] and development of the logistic model has been proposed as a solution [33]. This model accommodates individual variation as a decrease in mortality at advancing ages (i.e. individual frailty; frail individuals tend to die younger, leaving more robust individuals as survivors) [34–36]. Although these functions have been applied across a variety of species [37,38], support for them is mixed and it is often difficult to deduce whether uncertainty in parameter estimates is evidence of absence (the parameter is not important) or absence of evidence (the data do not provide a sufficient signal to help infer the parameter). Life histories can be split into distinct phases, each with an individual mortality signature. Caughley [39] identified three stages: juvenile (characterised by relatively high mortality), adult (with relatively low mortality), and senescent (increasing rates

of mortality in later life). When combined, these stages form a "U" shape or "bathtub" mortality curve, which can capture complex patterns of mortality over complete life histories (e.g. the Siler function [40]). The use of mortality trajectories and the separation of life stages allows us to unravel subtle changes in mortality and identify actuarial senescence, hereafter referred to as senescence. This combining of mortality models to accommodate different life stages has found support in a variety of species [41–43], and has helped to reveal some of the drivers [44] of age-specific patterns of mortality and senescent variation.

To evaluate the use of mortality trajectories and investigate patterns of age-specific mortality, we use data from a long-term study of a population of European badgers (*Meles meles*) naturally infected with *Mycobacterium bovis*, the causative agent of bovine tuberculosis (bTB). In the United Kingdom, badgers are the primary wild maintenance host for bTB [45], and in some locations contribute to the persistence of infection in cattle populations [46]. Being able to discern patterns of mortality and distinguish between groups in terms of disease susceptibility may help inform approaches to managing infection in badgers, thereby reducing risks of onward transmission to cattle. The epidemiology of bTB in badgers has been the focus of many studies (for a review, see [47]), yet the use of mortality trajectories, using age as a continuous variable, has to our knowledge been implemented only once. McDonald et al. [44] used Bayesian survival trajectory analysis (BaSTA) [48] to identify sex differences in mortality from the point of infection and infer the mechanisms underpinning them. Increased mortality as a result of bTB infection in male badgers is already known [11,24], but this was further dissected to identify where in the infection process the sex differences arose [44]. These analyses, however, do not capture the full lifetime trajectory of mortality in badgers, and cannot reveal actuarial senescence. Here, we study mortality trajectories by using cubs of known age and known infection status to analyse disease-related mortality trajectories across entire life histories. Previous analyses of badger mortality have suggested that badgers show no evidence of actuarial senescence [11], but these conclusions were based on static life table data, and so may not be an authentic representation of badger life histories.

In the following analyses, we use Bayesian approaches to demonstrate the benefits of using age-specific mortality trajectories to reveal when and how gender differences in disease-induced mortality occur. Research employing mortality trajectory analysis commonly recognises sex and individual heterogeneity [49,50] as critical drivers of mortality, although environmental variation has also been considered [23,51]. Males are often more susceptible to infection [52], have a weaker immune response [53], and greater disease-induced mortality [11,24], stemming from physiological variation [54] or behavioural and ecological differences that result in males being more likely to become infected [44]. Gender differences are not consistent across all species, and our understanding of the complex nature of sex influences on ageing patterns is far from complete [55]. Long-lived species are more likely to display negligible or negative patterns of senescence [56], but by using BaSTA to assess mortality trajectories, we uncover complex age- and sex-specific patterns of mortality that vary with infection status. We also reveal important limitations of standard mortality trajectory analysis for epidemiological research, including age-dependent predictors (disease state changes with age) and diagnostic uncertainty (tests for infection vary in their sensitivity and specificity towards the target pathogen [57]). We discuss alternative modelling strategies that will help to deal with these limitations.

2. Materials and Methods

2.1. Ecological Data

We used capture-mark-recapture (CMR) data from a population of wild badgers naturally infected with *Mycobacterium bovis* in Woodchester Park, Gloucestershire. Data for the present study consisted of badgers trapped from 1982 to 2015 inclusive. The badger population was sampled using live traps on (usually) four occasions per year. All trapped badgers were anaesthetized and subjected to several diagnostic tests for bTB before being released (for a more detailed account of

the trapping and testing procedures, see [58,59]). On first capture, each badger was given a unique identifying tattoo, so that it could be identified at subsequent captures. Data available in Supplementary material—Hudson_2019_MTA_Data.

2.2. Diagnostic Tests

Samples of sputum, faeces, urine, and swabs of any abscesses or wounds were taken for *M. bovis* culture [60], as well as blood samples obtained for antibody tests as follows:

- Brock ELISA (enzyme-linked immunosorbent assay) [61]—used from 1982 to 2006
- BrockTB Stat-Pak lateral flow immunoassay (Chembio Diagnostics Systems, USA) [62]—used from 2006 to 2015

We used badgers of known age (i.e. badgers caught as cubs) and categorised them as "cub-positive" if they tested positive to either the Brock ELISA, Stat-Pak, or culture during the first year of their lives, and "never-positive" if they never tested positive to any test throughout their lives (sex was also included as a categorical covariate for each group). The distinction between these two groups allows for the comparison of disease effects on mortality trajectories across entire life histories, and identification of where variations occurred. The analysis of age-dependent acquisition of disease requires a more complex modelling framework, but for this analysis we filtered out any badgers that acquired test-positive status beyond the first year of life (see discussion for commentary on the risk of bias). We also recognise that the diagnostic tests employed in this study have limitations in terms of their sensitivity (Brock ELISA: 40.7% [63]; Stat-Pak: 49%; culture: 10% [64], yet all the tests used are highly specific (Brock ELISA: 94%–98% [61]; Stat-Pak: 97%; culture: 100% [64]). As a result, we are confident that individuals diagnosed as infected are very rarely truly uninfected, but can be rather less confident that individuals diagnosed as uninfected are truly uninfected. Our classification of "never-positive" removes some of this uncertainty, as an individual is required to have tested negative throughout their capture history and is not reliant on a single diagnostic test result (see discussion for implications).

Ongoing research seeks to clarify links between diagnostic outcomes and infection status [65,66], but for the purposes of our analyses here, we worked with diagnostic results rather than true infection status.

Badgers caught and identified as cubs were assigned a birth occasion as the first trapping season for the year of first capture, as the majority of cubs are born between February and March each year [67]. Badgers recovered dead were assigned a known death occasion as the time of the post-mortem examination.

2.3. Analysis

To understand age-specific mortality patterns in badgers, and how their mortality trajectories are affected by diagnosis of bTB infection, we used the package BaSTA [48] in R [68]. This package implements a hierarchical Bayesian model (for full details and likelihood functions, see [30]) and draws inference on age-specific survival from CMR data when large portions of the data consist of unknown birth and death years. Age-specific survival analysis requires the definition of mortality or hazard rate: we define a random variable X for ages at death, where $X > 0$ with any given age, represented by (lower case) x. Standard theory of survival models defines the hazard function (μ) (i.e., the instantaneous rate of death [69], given survival to age x) as

$$\mu(x|\mathbf{b}) = \lim_{\Delta x \to 0} \frac{\Pr(x < X < x + \Delta x | X \rangle x, \mathbf{b})}{\Delta x}, \quad (1)$$

where **b** is a vector of mortality parameters to be estimated, and Δx is some very small time period. The cumulative hazard function (H) at age x, t years later is then defined as

$$H(x|\mathbf{b}) = \int_0^x \mu(t|\mathbf{b})\, dt, \tag{2}$$

From Equations (1) and (2), it is possible to derive the survival function (S) as

$$S(x|\mathbf{b}) = \Pr\{X > x|\mathbf{b}\} = \exp\left[-H(x\middle|\mathbf{b})\right], \tag{3}$$

and the probability density function (pdf) of ages at death as

$$f(x|\mathbf{b}) = \Pr\left(x \le X < (x + \Delta x)\right) = S(x|\mathbf{b})\, \mu(x|\mathbf{b}) \tag{4}$$

BaSTA allows for the comparison of four different functional forms of the mortality function in Equation (1) (Exponential, Gompertz, Weibull, and Logistic), as well as the extension of the latter three to incorporate more complex shapes. The inclusion of a "Makeham" [31] term models the effect of age-independent mortality (c). The further addition of a declining Gompertz function then allows the exploration of "bathtub" mortality shapes. In total, we compared ten different forms of mortality function (Table 1).

Table 1. Basic mortality and survival probability functions available to test in Bayesian survival trajectory analysis (BaSTA)—namely, exponential, Gompertz, Weibull, and logistic. Additional terms can be added to each model (except exponential) to test different shapes, namely "Makeham" and "bathtub". Parameter constraints are also indicated.

Model	Mortality Rate $\mu_b(x\|b)$	Survival Probability $S_b(x\|b)$	Parameters
Exponential	b_0	e^{-bx}	$b_0 > 0$
Gompertz [28]	$\exp(b_0 + b_1 x)$	$\exp\left[\frac{e^{b_0}}{b_1}\left(1 - e^{b_1 x}\right)\right]$	$-\infty < b_0,\ b_1 < \infty$
Weibull [29]	$b_0 b_1 (b_1 x)^{b_0 - 1}$	$\exp\left[-(b_1 x)^{b_0}\right]$	$b_0, b_1 > 0$
Logistic [33]	$\frac{\exp(b_0 + b_1 x)}{1 + \left(\frac{e^{b_0}}{b_1}\right) b_2 \left(e^{b_1 x} - 1\right)}$	$\left(1 + b_2 \frac{e^{b_0}}{b_1}\left(e^{b_1 x} - 1\right)\right)^{-\frac{1}{b_2}}$	$b_0, b_1,\ b_2 > 0$

The Makeham structure consists of adding a constant (c) to the mortality (μ_b) and survival rates (S_b) when **b** is a vector of parameters to be estimated and x is age:

$$\mu_b(x|\mathbf{b}, c) = \mathrm{c} + \mu_b(x|\mathbf{b}), \tag{5}$$

$$S_b(x|\mathbf{b}, \mathrm{c}) = \mathrm{e}^{-cx} S_b(x|\mathbf{b}), \tag{6}$$

with $\mathrm{c} > 0$ if $\mu(x)$ is declining or $\mathrm{c} > -\mu(0)$ otherwise. The bathtub structures are constructed by adding a declining Gompertz function and a constant to the basic mortality:

$$\mu_b(x|\mathbf{b}, \mathbf{a}, c) = e^{a_0 - a_1 x} + c + \mu_b(x|\mathbf{b}), \tag{7}$$

$$S_0(x|\mathbf{b}, \mathbf{a},\ \mathrm{c}) = \exp\left[\frac{e^{a_0}}{a_1}(e^{-a_1 x} - 1) - cx\right] S_b(x|\mathbf{b}), \tag{8}$$

with $-\infty < a_0 < \infty$, $a_1 > 0$, and $c > -[e^{a_0 - a_1 x_{min}} + \mu_b(x_{min}|\mathbf{b})]$, where x_{min} is the age at which Equation (5) is at its lowest value.

Examples of the shapes of mortality trajectory that can be defined by these models are shown in Figure 1.

The models in Table 1 define parameters and describe mortality in four different ways: (1) exponential, in which the model assumes mortality to be constant and independent of age; (2) Gompertz [28], in which the model describes baseline mortality (b_0) and an exponential increase with age (b_1); (3) Weibull [29], in which b_0 is the shape parameter and b_1 is the scale parameter, the model assumes that mortality increases (or decreases) as a power function of age; and (4) logistic [33], in which the model consists of an initial exponential increase in mortality that decelerates to a plateau after a particular age. The b_2 parameter describes the degree of deceleration in mortality with age. Bathtub variants of the models include a declining Gompertz function $e^{a_0 - a_1 x}$, where a_0 represents initial mortality rate at birth and a_1 is the exponential decrease in age-dependent mortality from birth.

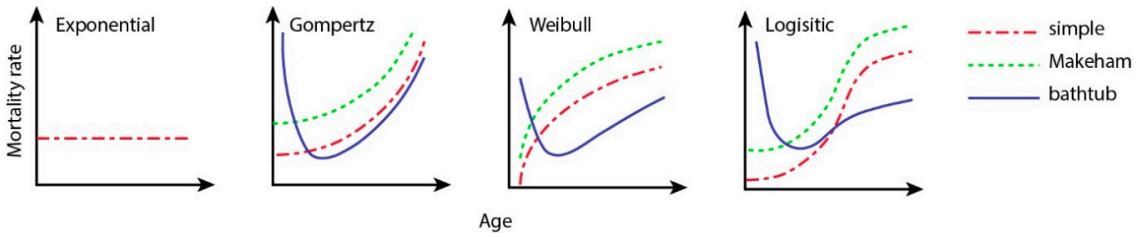

Figure 1. Possible mortality trajectories, $\mu(x|\theta)$ when θ is a vector of mortality parameters to be estimated, resulting from the four models included in BaSTA. Mortality or hazard rate is shown on the y-axis, with age as a continuous variable on the x-axis. The line styles represent examples of each model shape that are possible to test: simple, Makeham, and bathtub. The exponential model is only applicable in a simple format.

Badger sex and infection status ("cub-positive" or "never-positive") were included as categorical covariates and incorporated into the models as linear functions of the survival parameters—for example, in a Gompertz mortality function:

$$\mu(x|\theta) = \exp\left[\overbrace{\left(\alpha^T z\right)}^{b_0} + \overbrace{\left(\beta^T z\right)}^{b_1} x\right], \tag{9}$$

where α^T and β^T are transposed vectors of linear coefficients that link the covariate z with the survival parameters b_0 and b_1, such that $\theta = (\alpha, \beta)$. Covariates are included for all parameters in each model structure.

To ensure model convergence, initial trials of four Markov chain Monte Carlo (MCMC) chains were run for each model, followed by 1,000,000 iterations, with a burn-in of 10,001 iterations and thinning every 100 iterations [70]. Convergence was assessed visually, ensuring mixing of the chains, and formally within each model using the potential scale reduction ($\hat{R}$) [48]. Convergence is reasonable when $\hat{R} \approx 1$. We assessed the sensitivity of the mortality parameters to the choice of prior distributions [71] by running the analysis under four different prior structures, and found there to be no differences in the selection or identification of parameters as a result.

The fits of the ten models were compared using their deviance information criterion (DIC) [72], which is a measure of predictive power and criterion for model fit, akin to the Akaike information criterion and the Bayesian information criterion (for a review of its use, see [73]). To evaluate the impact of categorical covariates, BaSTA uses an adapted version of the Kullback–Liebler discrepancy [74,75], which estimates the degree of overlap in the posterior distributions of the parameter estimates. This indicator provides a value for $k_\beta \in [0.5, 1]$ for a given parameter β (0.5 indicating full overlap, 1 meaning no overlap); $k_\beta \approx 0.65$ is generally interpreted as indicative of a difference between means that is unlikely to occur if the distributions of the two variables are the same [76].

Recapture probabilities were modelled as fully time-dependent, allowing the parameter estimate to vary for each occasion. Sample sizes for each type of datum are provided in Table 2. R code available in Supplementary material—RMarkdown_BaSTA_code.

Table 2. Summary of capture-mark-recapture data sets describing badgers in one of two health states: "cub-positive" (badgers that tested positive in the first year of their lives) and "never-positive" (badgers that have never tested positive throughout their lives). Known birth years refers to cubs captured and identified as being within the first year of their lives. Known death years refers to badgers who were recovered dead and subjected to post-mortem. Detections are the total number of capture events that took place over the duration of the study.

Summary Statistic	Cub-Positive	Never-Positive
Total number badgers	428 (M 191; F 237)	1768 (M 833; F 935)
Number of known birth years	428	1768
Number of known death years	13	323
Total number of detections	2515	7588

3. Results

The Gompertz bathtub or Siler [40] function was the most supported mortality model across both the "cub-positive" (Figure 2a) and "never-positive" (Figure 2b) badger data sets, with substantial support as the "best" model and with a clear difference in DIC to the nearest rival model (Table 3). The Siler model is the sum of three different mortality models: the first describing a decrease in mortality over the initial phase of life, with e^{a_0} being the initial level and a_1 modelling the rate of decrease. The central "Makeham" term is a constant hazard, which is independent of age, and the final term is a Gompertz function, which describes mortality as increasing exponentially with a rate of b_1 from an initial level e^{b_0}.

Table 3. Ranked list of tested mortality functions, fitted to data from a wild population of European badgers naturally infected with bovine tuberculosis. Badgers were separated into two health states ("cub-positive": tested positive in the first year of their lives; "never-positive": never tested positive throughout their lives). Deviance information criterion (DIC) values are given for each model, as well as corresponding differences (ΔDIC) with respect to the "best" model. Substantial support for the "best" model is indicated when alternative candidate models have ΔDIC > 3 [73].

Cub-Positive (in Rank Order by DIC)				Never-Positive			
Model	**Shape**	**DIC**	**ΔDIC**	**Model**	**Shape**	**DIC**	**ΔDIC**
Gompertz	Bathtub	4622	0	Gompertz	Bathtub	25,678	0
Gompertz	Simple	4642	20	Exponential	Simple	25,693	15
Logistic	Bathtub	4661	39	Weibull	Bathtub	25,695	17
Weibull	Bathtub	4669	47	Weibull	Makeham	25,954	276
Weibull	Makeham	4675	53	Logistic	Makeham	25,975	297
Logistic	Makeham	4682	60	Logistic	Simple	25,982	304
Weibull	Simple	4689	67	Gompertz	Makeham	26,004	326
Logistic	Simple	4697	75	Logistic	Bathtub	26,048	370
Gompertz	Makeham	4710	88	Gompertz	Simple	26,136	458
Exponential	Simple	4741	119	Weibull	Simple	26,235	557

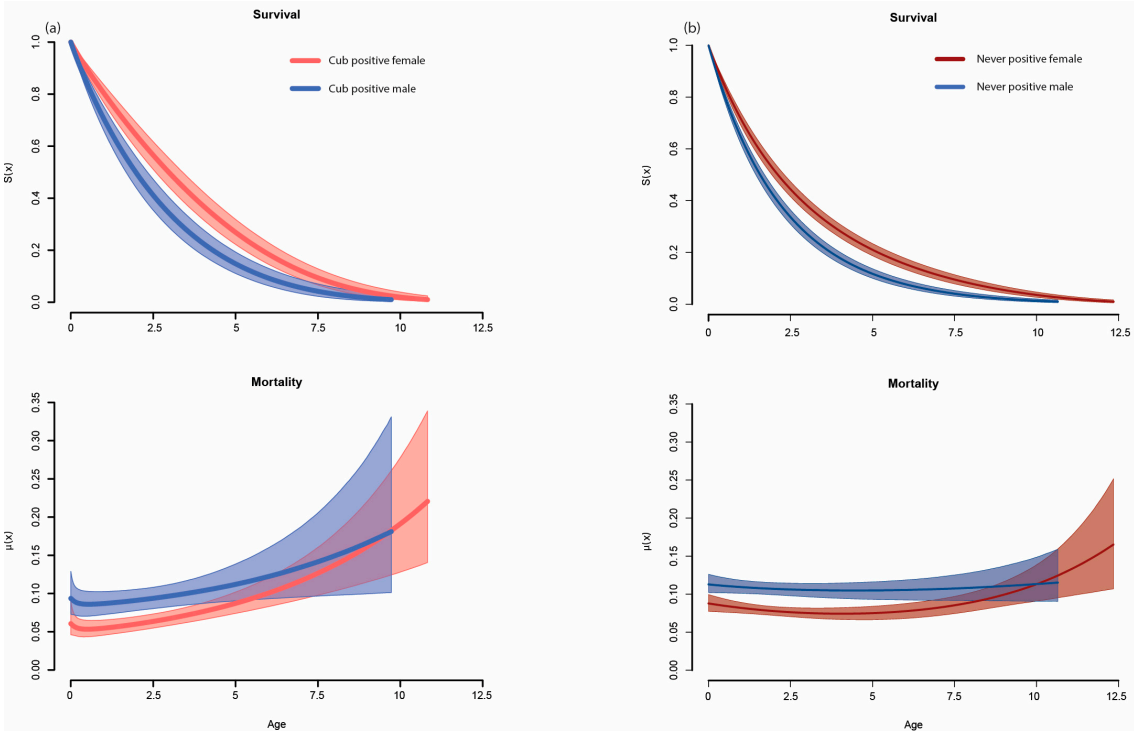

Figure 2. Age-specific survival and mortality trajectories of European badgers from a wild population naturally infected with bovine tuberculosis: (**a**) "cub-positive" individuals (badgers that tested positive in the first year of their lives) and (**b**) "never-infected" individuals (badgers that never tested positive throughout their lives). Female (red) and male (blue) estimated survival and mortality curves of the Siler function. Coloured areas surrounding the curve represent 95% credible intervals. Age in years.

Having revealed sex-, disease-, and age-specific patterns of mortality, we then analysed the entire data set using the Siler function, with disease status and sex as individual-level categorical covariates, creating four different groups (cub-positive male, cub-positive female, never-positive male, never-positive female). We assessed model fit by producing Kaplan–Meier plots of observed survival against predicted survival trajectories (Figure S1), and were satisfied that the Siler function and posterior parameter estimates were appropriate. We compared the posterior distributions between groups for each mortality parameter, both visually and using an adapted version of the Kullback–Liebler discrepancy [74] proposed by McCulloch [75] (Figure 3). The discrepancy measure works on the log of estimated probabilities, and due to the posterior densities of the a_1 parameters between "cub-positive" and "never-positive" female badgers being so different, the estimated probability produced zeroes, which in turn produced an NA in the Kullback–Liebler calculations.

Badgers diagnosed as infected shared very similar patterns of age-dependent mortality, with the only sex difference in mortality trajectories lying within the Makeham/age-independent parameter (c). "Never-positive" badgers displayed a greater degree of dissimilarity between the sexes. Male badgers had greater age-independent mortality (c) and initial "at birth" mortality rates (a_0), which follows previous research [11,76]; however, we also uncovered sex variation in the senescent phase (b_0 and b_1) of the mortality trajectory. "Never-positive" male badgers fail to display any evidence of a senescent decline in survival, whereas female badgers spend the majority of their lives with a comparatively lower mortality rate until the later phase of their lives, when they display a much clearer pattern of senescence. Infection raised the initial mortality rate (a_0) and intensified the senescent decline (b_1) in survival for both sexes, inducing a pattern of senescence in male badgers.

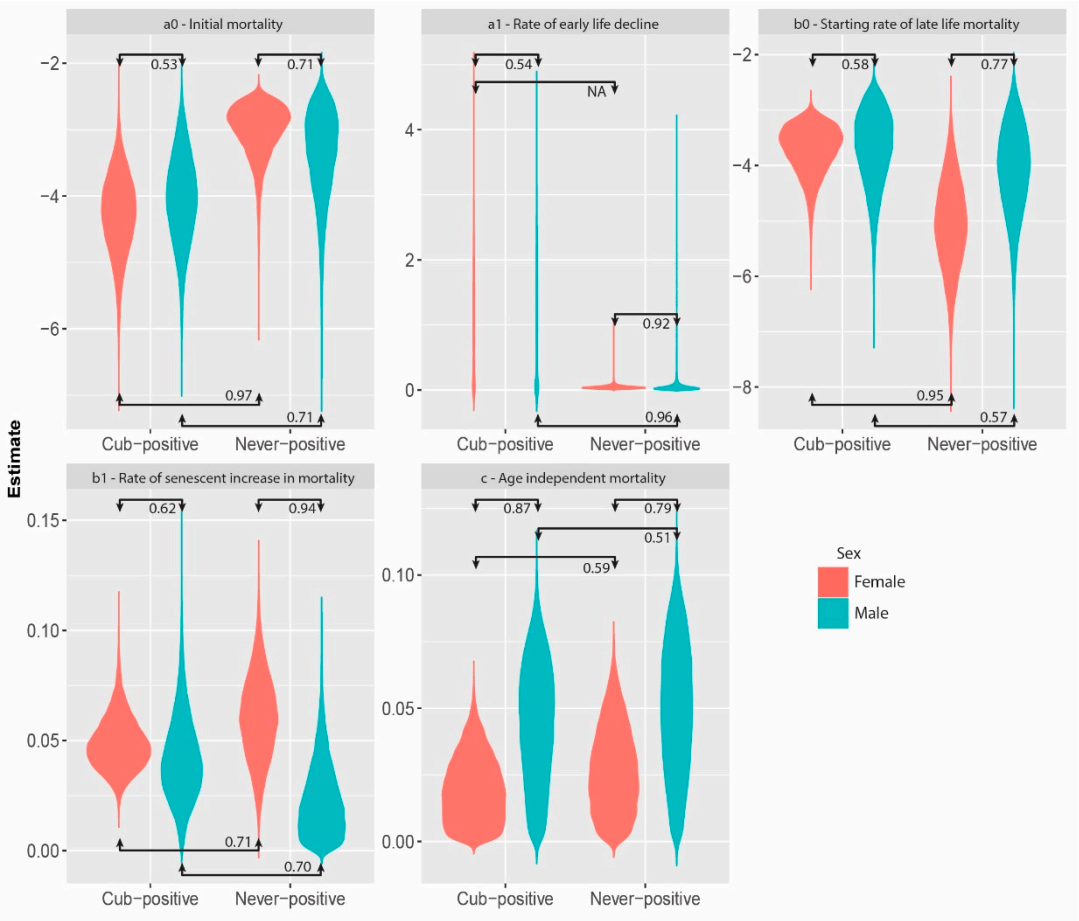

Figure 3. Posterior distributions of mortality trajectory parameter estimates for a population of wild European badgers naturally infected with bovine tuberculosis. Female (red) and male (blue) posterior distributions of mortality parameters of the Siler function, split by infection status. "Cub-positive" refers to individuals who tested positive in the first year of their life. "Never-positive" refers to individuals who never tested positive throughout their lives. Adapted Kullback–Liebler discrepancy measures are shown in black, indicating the degree of distribution overlap between classifications of sex and disease status. Measures over 0.65 are considered important (0.5 = distributions are identical, 1 = no overlap). Iterations = 1,000,000; burn in = 10,001; thinning = 200; number of chains = 4. (For table of estimates and 95% confidence intervals, see Table S1).

The parameter estimates also uncovered a lack of any real decline in mortality during the juvenile phase of the life history (a_1) for "never-positive" individuals (male $a_1 = 0.05$, female $a_1 = 0.06$), as well as extremely flat posteriors for "cub-positive" individuals, suggesting a lack of certainty. This pattern of mortality is further supported by the second "best" model, being the simple exponential ("never-positive") and simple Gompertz ("cub-positive"), neither of which define an initial phase of reducing mortality for uninfected badgers.

4. Discussion

Mortality trajectory analysis has revealed complex, age-specific patterns of mortality, and provided evidence of actuarial senescence in badgers, a species previously believed to display near-constant rates of mortality throughout life. Our results discern the impact of bTB infection on wild badgers, and has allowed us to estimate where in a species' life history disease- and sex-differences occur.

The inclusion of age as a continuous variable enabled us to generate mortality trajectories and clarify age-specific sex differences. In our case study, we found "never positive" male badgers to have a higher initial mortality rate (compared to females), which appears to decline with age, yet

"never-positive" females show a more intense increase in later life (senescence). Higher rates of mortality in males resemble the sex bias evidenced across other mammalian species [77]. Explanations for higher rates of mortality among males include differences in intra-sexual reproductive competition [78], physiology [54], behaviour [79], and ecology [80]. In addition to an age-independent sex difference, the male bias in juvenile mortality hints at differences in physiology being the key driver: although behavioural differences could appear, ecological explanations are unlikely to have come into effect at this early stage of a badger's life. An unanticipated result was the more intense senescent increase in mortality with age found in female badgers. Males do not live as long as females (11% reduction in lifespan irrespective of infection status), and it is possible that this reduced lifespan removes or reduces the potential to exhibit detectable signs of senescence. There is a growing body of evidence reporting sex differences in senescence (e.g., [81,82]), with the majority indicating a greater effect in males. A number of reasons have been proposed, mostly associated with a greater impact of sexual selection in males, although this has been challenged in a study of herbivores [83]. The pattern of "never-positive" male mortality found here is more in line with previous findings that show negligible actuarial senescence in badgers [44].

It was already known that bTB infection, as indicated from several diagnostic tests, results in increased male mortality in badgers [11,24], but our analysis provides evidence for a similar effect in females. Mortality trajectories of the "cub-positive" individuals revealed novel patterns of senescence and indicated that infection promotes a senescent increase in late-life mortality; this effect is more pronounced in male badgers, thus homogenizing the shape of the mortality trajectories and removing any signature of age-dependent sex differences. Recent work has revealed a diversity of age-specific patterns of mortality, both within and amongst species [35], with sex and individual differences in frailty being highlighted as the most important sources of variation in survival parameters [84]. Our analyses found only limited support for individual heterogeneity amongst badgers, indicated by the low ranking of the logistic model (third for infected badgers and fifth for uninfected). Males and females, on the other hand, do display differences in individual heterogeneity, and may in fact be better described by sex-specific models [27]. Our combined sex analysis may have masked such variation, suggesting that any reduction in mortality with advancing age could be representative of real change [34], or be an artefact of heterogeneity among individuals in the population [33]. Previous studies have suggested that ignoring frailty may result in biased parameter estimates, but with only moderate support for the logistic mortality model it is difficult to draw any firm conclusions. Should individual heterogeneity in frailty exist, then the more frail individuals with higher mortality should be removed from the population as a result of within-cohort selection [85]. The lack of evidence for individual heterogeneity in the present study may in part be due to aspects of badger ecology. Most badgers give birth between mid-January and mid-March [86], then cubs spend their first few weeks underground and are unavailable for capture. Previous research has estimated pre-capture mortality at 24% [67], and perhaps it is at this stage when the majority of weaker individuals are lost from the population. Pre-capture mortality has not been included in our analysis, and with trapping not taking place during March and April, cubs may be upwards of 6 months old when they are first captured and tested for bTB. Consequently, our estimates of initial mortality are likely to be underestimates, and in reality, the downward curve assumed in the juvenile phase of the Siler function would be more pronounced than presented here.

We used the package BaSTA, with age-specific survival data and a hierarchical structure within a Bayesian framework, to draw inference from censored CMR data, in order to investigate survival and mortality in a badger population naturally infected with bTB. Our study has demonstrated the benefits of this approach to mortality trajectory analysis for the study of wildlife disease epidemiology, and clarified age-specific sex and disease variation in patterns of mortality. There are, however, inherent weaknesses in our modelling framework, and to overcome them will require a more flexible modelling approach. BaSTA dictated our categorisation of badgers into two fixed groups of "cub-positive" and "never positive" individuals, as it is unable to assess the influence of time-varying disease states

on mortality parameters. This restriction meant filtering out badgers that first tested positive after their first year of life, and leaves unanswered questions regarding the mortality trajectories of such individuals. The inability to model time-varying disease states also forced us to use a binary disease classification. Recent research into the epidemiology of bTB in badgers has identified at least four different states of infection (susceptible, test positive, single site excretor, multi-site/occasion excretor), with differing mortality rates at each stage [11], and high levels of individual heterogeneity in disease progression over time [24]. This adds further complexity, and suggests the potential for differing mortality trajectories at each disease state, as well as for each age-at-infection/state—if, for example, older badgers are more likely to become infected and experience more rapid disease progression. To model this system more completely will require a more flexible multi-state framework that allows for time-varying transition through multiple disease states. Further complications relevant to studies of bTB are the limitations of diagnostic tests and changes in the prevailing tests employed in studies over time [63,87]. False-positive diagnoses would potentially weaken the signal of mortality in "cub-positive" badgers, whereas the more likely false negatives could strengthen the signal in the "never-positive" individuals. Our results may therefore be more conservative for "cub-positive", yet potentially overstated for "never-positive" individuals. We are confident that any impact is minimal, due to tests being highly specific (low chance of false-positive) and recapture being common, with an average of 5.9 capture/testing occasions per badger (therefore reducing the chance of any individual being wrongly included in either category). There was no bias in the recapture rate between categories, which reduces any impact of selective disappearance. The issue of test performance could be explicitly addressed by the further development of mixture models that can incorporate diagnostic uncertainty generated from false-positive and false-negative test results [57]. Multi-event methods have been developed to deal with such problems [17,88,89], often implementing the software package E-Surge [90]. To fully address all the difficulties outlined here requires the combination of these methods and a need to develop more complex, hierarchical state-space models developed from first principles, using MCMC software such as BUGS, JAGS, or Stan, which also allow for the inclusion of age as a continuous covariate.

We have demonstrated the use of relatively simple mortality trajectory analysis in the study of wildlife disease epidemiology. We recommend widespread use of this approach in systems that have sufficient information to infer patterns of mortality across the whole life cycle. Despite senescence being notoriously difficult to detect in wild populations [25], the present study has provided credible evidence of actuarial senescence in badgers. Furthermore, it has revealed that senescence can be intensified in diseased individuals. Understanding the physiological, evolutionary, and ecological drivers of these mortality trajectories remains an ongoing challenge [23]. BaSTA is a powerful tool to begin exploration whilst accommodating many of the problems associated with CMR data. However, there are limitations associated with age-dependence and diagnostic uncertainty of disease states, and we are now developing similar Bayesian methods with more complex hierarchical and multi-state frameworks.

Supplementary Materials: The following are available online at http://www.mdpi.com/1424-2818/11/10/182/s1, Figure S1: Kaplan–Meier plots (in red) of observed survival on top of predicted survival trajectories and 95% confidence intervals for a population of European badgers naturally infected with bovine tuberculosis, split by sex and infection status: (a) "cub-positive" females; (b) "cub-positive" males; (c) "never-positive" females; (d) "never-positive" males. Table S1: Posterior parameter estimates, standard deviations, and lower/upper 95% confidence intervals of mortality trajectories for a population of wild European badgers naturally infected with bovine tuberculosis. R Code: RMarkdown_BaSTA_code. Data: Hudson_2019_MTA_Data.

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