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Genetic, social and maternal contributions to *Mycobacterium bovis* infection status in European badgers (*Meles meles*)

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Abstract

Within host populations, individuals can vary in their susceptibility to infections and in the severity and progression of disease once infected. Though mediated through differences in behaviour, resistance or tolerance, variation in disease outcomes ultimately stems from genetic and environmental (including social) factors. Despite obvious implications for the evolutionary, ecological and epidemiological dynamics of disease traits, the relative importance of these factors has rarely been quantified in naturally infected wild animal hosts. Here, we use a long-term capture–mark–recapture study of group-living European badgers (*Meles meles*) to characterize genetic and environmental sources of variation in host infection status by *Mycobacterium bovis*, the causative agent of bovine tuberculosis (bTB). We find that genetic factors contribute to *M. bovis* infection status, whether measured over a lifetime or across repeated captures. In the latter case, the heritability (h^2) of infection status is close to zero in cubs and yearlings but increases in adulthood. Overall, environmental influences arising from a combination of social group membership (defined in time and space) and maternal effects appear to be more important than genetic factors. Thus, while genes do contribute to among-individual variation, they play a comparatively minor role, meaning that rapid evolution of host defences under parasite-mediated selection is unlikely (especially if selection is on young animals where h^2 is lowest). Conversely, our results lend further support to the view that social and early-life environments are important drivers of the dynamics of bTB infection in badger populations specifically, and of disease traits in wild hosts more generally.

KEYWORDS

bovine tuberculosis, infection status, *Meles meles*, *Mycobacterium bovis*, quantitative genetics

1 | INTRODUCTION

Pathogens and parasites are key drivers of the ecological and evolutionary dynamics of their wild host populations (Schmid-Hempel, 2011). In response, hosts have evolved a myriad of defence strategies that include behavioural avoidance of infection (Behringer et al., 2006), immune responses that limit parasite growth (resistance; Rigby et al., 2002), and repair of parasite-induced damage to minimize costs of infection (tolerance; Medzhitov et al., 2012). However, there can be considerable variation amongst individuals

in these traits which gives rise to differences in susceptibility to infection and the subsequent progression of disease. The importance of among-individual variation for population-level processes has become increasingly clear in recent years (e.g., Grist et al., 2014; Madritch & Hunter, 2002; Svanbäck et al., 2015), particularly with respect to our understanding of infection dynamics (Kramer-Schadt et al., 2009; van der Waal & Ezenwa, 2016). However, while among-individual variation can generally be viewed as stemming from both genetic and environmental (including social) effects, we currently have little knowledge of their relative importance in wild and unmanaged host populations where environmental factors can exert considerable influence on infection dynamics.

From an evolutionary point of view, parasites (in which we include pathogenic bacteria, viruses, fungi, protozoa and macroparasites) are expected to select for improved host defences. However, any response to selection is contingent on the presence of genetic variance in the host. A partial genetic basis of variation in host defence strategies against infectious disease is well-established in humans, model organisms and livestock studies (Breitling et al., 2008; Morris, 2007; Yan et al., 2006). For instance, selective breeding for resistance to specific parasites is important to agriculture and aquaculture (Stear et al., 2001; Yáñez et al., 2014). In addition to enabling host selection responses, genetic variation among individuals may also impact on parasite transmission dynamics, and patterns of disease emergence and prevalence (Doeschl-Wilson et al., 2011; Yates et al., 2006) with consequences for host behaviour, mortality and fecundity. Among-host genetic variation can therefore influence the population-level (demographic) consequences of infection through multiple routes (Lough et al., 2015; Nath et al., 2008).

At present, relatively little is known about the extent of genetic variation in disease susceptibility in wild host populations. This is largely due to the difficulties of obtaining appropriate immunological data coupled to genetic information (e.g., pedigree or relatedness measures over multiple generations). Several quantitative genetic studies have investigated variation in avian immune response traits, with findings ranging from an apparent absence of genetic effects (Pitala et al., 2007) to moderate heritability (h^2, the proportion of variance explained by additive genetic effects) of immune function (e.g. phytohaemagglutinin response in house sparrows, *Passer domesticus*, h^2 ($\pm$ *SE*) = 0.46 $\pm$ 0.19, Bonneaud et al., 2009; in common kestrels, *Falco tinnunculus*, $h^2 = 0.47 \pm 0.10$, Kim et al., 2013). Genetic variation in resistance and tolerance to ectoparasites has been reported in a cyprinid fish (*Leuciscus leuciscus*; Blanchet et al., 2010; Mazé-Guilmo et al., 2014), while analyses of helminth infection in Soay sheep (*Ovis aries*) revealed genetic variation in host resistance but not tolerance (Hayward, Garnier, et al., 2014; Hayward, Nussey, et al., 2014). There is also growing evidence that consistent differences in host behaviours, likely to influence infection risk (e.g., dispersal, sociability; Barber & Dingemanse, 2010), are heritable in natural populations (Korsten et al., 2013; Petelle et al., 2015). However, whether this behavioural variation represents an important source of genetic variation in infection status remains to be determined.

As studies to date have yielded mixed conclusions about the importance of genetic variation in disease traits in wild animal hosts, we also have limited understanding of how environmental factors contribute to among-host variation. Abiotic factors (e.g., rainfall, seasonality) can play an important role in shaping disease dynamics at the population level (Altizer et al., 2006), as can biotic environmental influences such as the distribution and social structure of host populations (Keiser et al., 2018). However, social effects, broadly defined as influences of phenotype arising from interactions with conspecifics, are also strongly associated with heterogeneity in disease dynamics. On the one hand, transmission of pathogens within groups of closely interacting individuals is thought to represent a major cost of group living (Kappeler et al., 2015). On the other hand, social immunity processes—whereby the immune response of one individual offers protection to group members—can sometimes occur (e.g., in Nicrophorus burying beetles; Palmer et al., 2016). More generally, social systems in which close-knit groups have limited among-group contact can inhibit the spread of disease over larger (among-group) scales (e.g., Delahay et al., 2000; Rozins et al., 2018).

The importance of social effects on disease traits can also change with age, precisely because social behaviours and contexts are themselves frequently age- or stage-specific. For example, sexually transmitted infections may be prevalent in a population, but be restricted to adults that engage in sexual activity (Rhule et al., 2010). Earlier in life, parental effects arising from interactions of offspring with parents (and/or helpers in cooperative systems) can influence both exposure and infection risk. In birds and mammals, for instance, immunocompetence in early life can depend entirely on the transfer of maternal antibodies (Grindstaff et al., 2003, 2006). More generally, environmental effects on maternal state (e.g., food availability) will influence investment in care, with downstream consequences for offspring immune development and disease resistance (Garbutt et al., 2014; Karell et al., 2008). A common finding across other trait types (e.g., growth, morphology, life history; Wilson et al., 2005; Houde et al., 2015; Falica et al., 2017) is that the importance of maternal effects as a source of phenotypic variance declines with (offspring) age (while h^2 often shows the opposite pattern). However, this does not mean that adult phenotypes should be assumed to be free from early-life influences (see e.g., Clark et al., 2014) and 'silver spoon' effects on later health are certainly well documented in the context of non-communicable diseases (Gluckman & Hanson, 2004).

Here, we examine the relative importance of genetic and environmental (including social and maternal) sources of variation in *Mycobacterium bovis* (the causative agent of bovine tuberculosis; bTB) infection status in a wild population of European badgers (*Meles meles*). Badgers are an important wildlife reservoir for bTB in the United Kingdom, where the disease in livestock is a longstanding socioeconomic burden on the industry and taxpayers (Defra, 2014). The primary route of infection in badgers is thought to be inhalation of infectious aerosol, occurring during close contact with infectious individuals (Gallagher & Clifton-Hadley, 2020). Some of

the drivers of disease in badgers have been described, such as sexual dimorphism, whereby bTB infection probability, disease progression and mortality risk are all greater in males (Graham et al., 2013; McDonald et al., 2014). Age effects have also been observed (Beirne et al., 2016; Graham et al., 2013; McDonald et al., 2014), while at the population level, bTB incidence and prevalence exhibit seasonal variation (incidence being highest in spring and prevalence peaking in autumn; Delahay et al., 2013). However, the potential contribution of additive genetic variation has not previously been investigated, not least because badgers live in kin-biased social groups making disentangling genetic from environmental (social) effects challenging.

Badgers are facultatively social, forming groups in medium- to high-density populations but adopting a more solitary lifestyle when living at low density (Roper, 2010). At the level of the population, natal philopatry and territorial defence limit mixing of animals amongst social groups, which in turn is expected to reduce intergroup disease transmission (Delahay et al., 2000), while at the same time being associated with relatively high within-group transmission rates. Social group structure should thus drive spatial clustering of bTB, and high among-group variation in disease status, relative to that found within groups, has been previously reported (Delahay et al., 2000). However, genetic data suggest alternative explanations for observed spatial clustering may also have merit. Parentage analyses show that among-group breeding dispersal is limited, leading to greater relatedness within than among groups (Dugdale et al., 2008). Crucially for current purposes though some individuals are known to make permanent moves away from their natal group (Rogers et al., 1998) while breeding between adults of different groups also occurs (Annavi et al., 2014; Marjamäki et al., 2019). For instance, in this population an estimated 37% of cubs born are sired by an extra-group male (Marjamäki et al., 2019). Recent work has also shown that bTB infection risk for cubs is increased by the presence of closely related infected adults (including but not limited to mothers) within the natal group (Benton et al., 2016). Spatial heterogeneity in host disease status is consistent with within-group (and by extension kin-biased) social interactions impacting infection risk, maternal effects, and/or genetic variation in one or more host defence strategies. These alternative explanations are in no sense mutually exclusive and we also acknowledge that inbreeding depression (IBD) could play a role (e.g. if breeding dispersal and therefore inbreeding differ among groups; Benton et al., 2016). Heterozygosity–fitness correlations have provided some evidence of IBD on *M. bovis* disease progression although this is limited to older (senescent) females (Benton et al., 2018).

It is therefore clear that *M. bovis* infection status in badgers can be influenced by numerous factors at multiple scales. The long-term life-history and genetic pedigree data from the Woodchester Park study initiated in the 1970s (McDonald et al., 2018) afford a rare opportunity to assess the relative importance of genetic and environmental effects. We adopt a quantitative genetic animal model approach to decompose the variance in bTB infection status into its component parts and examine the relative contributions of genetic and environmental factors. We ask: (a) whether variation in host infection status has a detectable additive genetic basis; (b) what are the relative contributions of additive genetic and social (including maternal) effects on the observed variation in host bTB status; and, (c) do the relative contributions of additive genetic and social effects on bTB status vary in relation to host age?

2 | METHODS

2.1 | Study site and sampling

A population of approximately 200–300 wild badgers has been the subject of an ongoing capture–mark–recapture study at Woodchester Park (Gloucestershire) since 1976. The study area is approximately 11 km^2 and consists of a steep-sided wooded valley surrounded by farmland, set in an area where *M. bovis* infection is endemic in cattle and wildlife. Badger dens (setts) in the study area have been the focus of trapping operations up to four times a year. During each quarterly 'trap-up', badgers are trapped for two consecutive nights using steel mesh box traps baited with peanuts, (after 4–8 days of pre-baiting). Trapped badgers are anaesthetized (de Leeuw et al., 2004) and their capture location, sex and age class (cub, yearling, adult) recorded. Biological samples are collected to allow determination of *M. bovis* infection status and to provide a DNA source for microsatellite genotyping (full details presented below). After a recovery period, all badgers are released at the point of capture. Social group boundaries are also determined for each year of the study by bait marking (Delahay et al., 2000). Further details on determination of group membership are discussed in Marjamäki et al. (2019) and references therein.

Overall, the mark–recapture data set used here contained 14,846 observations of *M. bovis* infection status on 2,945 individual badgers captured between 1976 and 2014. For individuals first caught as cubs or yearlings (readily identifiable from size, pelage and toothwear; Delahay et al., 2013), age at subsequent captures is known. Unsurprisingly, the age distribution is highly skewed (Figure 1); cubs, yearling and adults (i.e. age ≥ 2) account for 31.8%, 24.4% and 43.8% of observations, respectively. Among known-age adult captures, the modal age is 2 years (which accounts for 32.9% of adult observations) and the mean is 4.06 (SE 0.03) years. At all ages, the capture records are numerically dominated by putative uninfected animals (based on a recorded infection status score of zero; explained in full below). The data included 398 individuals first captured as adults for which ages were unknown. However, since capture records for individuals span multiple years, they still contain valuable information about within-individual changes with advancing age. In order to retain these individuals for analysis, we elected to assume that age = 2 years at their first capture. This is both the most likely true age (based on the distribution of known-age individuals) and also represents the minimum possible age (as cubs and yearlings are readily distinguished).

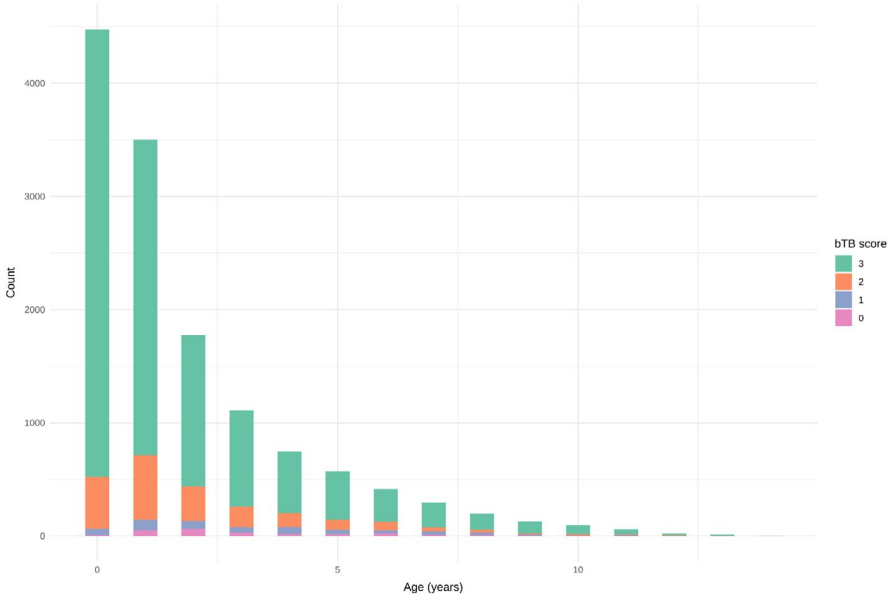

FIGURE 1 Histogram of *Mycobacterium bovis* infection status records by age and infection status score $bTB_{capture}$. Note that individuals may contribute multiple records (within and across ages), and only records of known-age badgers are included. Badgers have known age at capture if fist sampled as a cub (age 0) or yearling (age 1)

2.2 | Microsatellite genotyping and parentage analysis

Guard hairs taken at capture were used for DNA extraction, allowing microsatellite genotyping and parentage analysis. Full details are described in Marjamäki et al., (2019). Briefly, DNA was extracted from hair samples using either the protocol outlined in Carpenter et al., (2005), or an ammonium acetate extraction method (Richardson et al., 2001). We used a minimum of five hair follicles with visible roots per individual for extraction. Individuals were genotyped using a minimum of 16 (Carpenter et al., 2005) and maximum of 22 fluorescently labelled autosomal microsatellite markers. We used a 2 μl Qiagen Multiplex PCR reaction (Qiagen Inc., Valencia, USA), before separation of the amplicons on an ABI 3,730 DNA Analyzer and genotype scoring using GENEMAPPER 3.7. Microsatellite genotypes and spatial data were then used for Bayesian parentage analysis performed using the R 3.3.0 (R Core Team, 2019) package *MasterBayes* 2.54 (Hadfield et al., 2006). Markov chains were run separately for each year (i.e., cub cohort) for 2 million iterations, with a thinning rate of 100 and burn-in period of 500,000. Tuning parameters were specified for each cohort to ensure that the Metropolis–Hastings acceptance rates were within acceptable limits (0.2–0.5; Hadfield, 2017). The presence of unsampled males (per population) and females (per social group) was also allowed for each cohort. Assignments were accepted and used in downstream analyses when a confidence threshold of 80% was met, resulting in a total of 1,175 parentage assignments (579 maternities and 596 paternities). A total of 617 cubs were assigned at least one parent (35% of genotyped cubs included in the analyses), and of these, 556 (89%) were assigned both parents. Marjamäki et al. (2019) provide a thorough description of available pedigree information (see also archived data for this paper). The genetic pedigree is far from complete which may have implications for our analyses (as discussed below). We note that, in contrast to comparable long-term avian and mammalian studies, maternal identities cannot be determined by observation in badgers owing to their nocturnal and fossorial habits. Thus, pedigree analysis is especially challenging because maternities must be estimated simultaneously with paternities based on genetic and spatial data in the presence of multiple related candidate mothers and fathers.

2.3 | Infection status

For each captured badger, *M. bovis* infection status is determined from the bacterial culture of a standardized set of clinical samples (as described in Clifton-Hadley et al., 1993), and a serological test for the presence of antibodies to *M. bovis* (Brock Elisa used 1982 to 2006 (Goodger et al., 1994) and BrockTB Stat-Pak test used 2006 to 2014 (Chambers et al., 2008)). Clinical samples of oesophageal and tracheal aspirates, urine and faeces, are collected from all animals, with additional samples collected by swabbing open bite wounds if present. Results of these diagnostic tests are used to assign badgers to one of four bTB infection status categories on an ordinal scale following Graham et al. (2013). Individuals that returned negative results for both the bacterial culture and serological test were classified as test negative (N) and treated as free of infection. Badgers that tested antibody-positive but had negative culture results were assigned test-positive (P) status, taken to indicate recent exposure to *M. bovis*. Positive test results could also indicate cross-reaction or presence of maternal antibodies (Maas et al., 2013; but see Tomlinson et al, 2012). To account for this possibility, and reduce the false positive rate, we elected to reclassify single test-positive results as *N* (i.e., test negative) if individuals (a) had one or more subsequent recapture(s) and (b) all subsequent tests were negative. Badgers that tested positive for the presence of *M. bovis* by bacterial culture were assigned as either one-site (O) or multi-site (M) excretors, based on the number of sampled body sites (i.e., distinct clinical samples) that tested positive at each capture. Although culture has relatively low

sensitivity as a diagnostic test, a positive result is a strong indicator of established bTB infection (Drewe et al., 2010). These latter two categories (O, M) are therefore considered to represent more advanced infection states.

2.4 | Quantitative genetic analyses

To model variation in infection status, we defined two different response variables. Firstly, we reduced infection status data for each individual to a single binary 'lifetime' score ($bTB_{lifetime}$). Thus, each individual has a single observation of either 0 (if they did not test positive for bTB during their entire recorded lifetime) or 1 (if they did). Secondly, we analysed the repeated measures collected on individuals over multiple trapping events, to investigate the possibility that contributions of genetic and/or environmental effects to variance in infection status are age-dependent. Based on models of bTB immunopathogenesis in badgers (Lesellier et al., 2008; Mahmood et al., 1987), we assumed the four infection status categories described above can reasonably be ordered to reflect the progression of bTB within a host. We thus converted them to a numerical score ($N = 0$, $p = 1$, $O = 2$, $M = 3$) which we refer to hereafter as $bTB_{capture}$. Each individual thus has a number of $bTB_{capture}$ records equal to its number of captures during the study. We elected to make $bTB_{capture}$ score progressive, whereby values can increase (or remain constant) for an individual but cannot decrease. Both $bTB_{lifetime}$ and $bTB_{capture}$ were analysed in conjunction with pedigree information using 'animal models' (i.e. linear mixed effect models that include a random effect of an individual's additive genetic merit; Wilson et al., 2010) to estimate additive genetic variance (V_A). Variance components attributable to specified environmental effects were also estimated, and fixed effects were included (as specified below) to control for several known sources of variance not directly relevant to the current hypotheses. Note that fixed effect results are not presented or discussed in detail but are shown in full in the Supporting Information.

2.5 | Modelling lifetime bTB status

$bTB_{lifetime}$ was modelled using a Bayesian animal model implemented using the package *MCMCglmm* 2.26 (Hadfield, 2010) in R 3.6.1 (R Core Team, 2019). Sex was included as a fixed effect together with a cubic function of age at last capture. All else being equal, we would expect the probability of $bTB_{lifetime} = 1$ to increase monotonically with observed lifetime (even if risk of infection is not itself age-dependent) but a cubic function was chosen simply to avoid making strong assumptions about the functional form of the relationship. The additive genetic merit, maternal identity, natal group and birth year were included as random effects. We also included a (natal) group x birth year interaction. All random effects are assumed to be drawn from distributions with zero means and variances to be estimated of V_A, V_M, V_{NGr}, V_{BY} and V_{NGrxBY}, respectively. Note that 'group' designations are based on sett locations that are consistent across the timeline of the study. Consequently, any variance explained by (natal) group is likely to reflect spatial heterogeneity within the study area. In this model, V_{NGrxBY} serves (albeit imperfectly) to identify sets of individuals that clustered strongly in both space and time (i.e., same cohort and same spatial location). Note that we assumed the natal group is the group where badgers first sampled as a cub or yearling were found. We elected to exclude badgers with missing predictors from this analysis which, in practice, meant exclusion of individuals first caught as adults (as they had missing natal group information, even after assumptions about age at last capture). Additionally, several (3) individuals captured only once as cubs with missing sex data were excluded. However, we did include individuals with unknown mothers subject to all other predictors being available. Since the mother is unknown for the majority of individuals, this was a necessary compromise. Consequently, we ran this model on a data set comprising 2,319 badgers of which 606 (23.7%) have $bTB_{lifetime} = 1$.

The Markov chain was run using the 'ordinal' family (which uses a probit link for binary data) with residual variance fixed to 1. We used a parameter-expanded priors for random effects as suggested in Hadfield, 2019; more specifically parameter-expanded X^2 priors (by specifying V = 1, nu = 1,000, alpha.mu = 0, alpha.V = 1) and normally distributed diffuse priors for fixed effects. Convergence of the MCMC chain was checked using Heidelberger and Welch's convergence diagnostic test for stationarity (implemented in the R package *coda 0.19–3*; Plummer et al., 2006), and the level of autocorrelation checked to ensure adequate (>1,000) effective sample size for each estimated parameter. To enable more intuitive biological interpretation, estimated variance components (conditional on fixed effects) on the latent scale were transformed to the corresponding intra-class correlations values (i.e., including heritability, h^2) on the observed scale. This was done using the functions 'QGparams' and 'QGicc' from the R package *QGglmm 0.7.4* and the model 'binom1.probit' (de Villemereuil et al., 2016).

2.6 | Modelling bTB status with age

We then modelled $bTB_{capture}$ on the observed (0–3) scale using a series of animal models fitted by REML in *ASReml-R* 4 (VSN International). In all models, we assume Gaussian residuals, an assumption that is necessarily violated given that the response variable is bounded. While some caution with respect to our statistical inference is thus appropriate, we nonetheless consider this assumption very reasonable as residuals from all models showed unimodal distributions with strong central tendencies. We also note inferences from linear mixed models are relatively robust to even large departures from distributional assumptions (Schielzeth et al., 2020). Significance of fixed effects was determined using conditional Wald *F* tests, while statistical inference on random effects was by likelihood ratio test (LRT) comparison of the full model to reduced formulations in which the tested random effect was omitted. Twice the difference in log-likelihood between the full and reduced models was assumed to

have a χ^2 distribution. Following Visscher (2006), we assumed the test statistic to be asymptotically distributed as an equal mix of ${\chi_0}^2$ and ${\chi_1}^2$ (denoted as ${\chi_{0.1}}^2$) when testing a single variance component.

We sought to estimate age-specific quantitative genetic parameters for $bTB_{capture}$ for two reasons. First, we wanted to determine whether the relative contributions of genetic and environmental effects to variance change with age. Second, since $bTB_{capture}$ can increase (but not decrease) across observations within individuals, we expect among-individual variance (partitioned as additive genetic and/or permanent environmental variance) to increase with age (at least initially). Variance compounding is thus expected from trait definition as effects on the phenotype of any individual at age *x* will have 'permanent' effects (i.e., impact phenotype at all ages > *x*). We wanted our models to accommodate this feature of the data and to ensure that compounding of environmental variance could not cause upward bias in the estimate of additive genetic variance at later ages. In principle, an initial increase in among-individual variance with age would be followed by a decrease among the oldest badgers if infection and disease progression were inevitable consequences of sufficient longevity. In this scenario, badgers living long enough would eventually all converge on a single phenotype ($bTB_{capture} = 3$). However, this does not happen here and across all ages observed records are strongly dominated by captures of putatively uninfected badgers (i.e., $bTB_{capture} = 0$; Figure 1). For instance, in cubs, yearlings, all adults (age ≥ 2) and 'older' adults (age ≥ 4) the proportions of capture records with $bTB_{capture} = 0$ are 88.3%, 79.6%, 76.2% and 75.1%, respectively.

We adopted two complementary strategies to incorporate this age specificity of variance components. The first was to analyse stage-specific data subsets corresponding to cubs (age = 0; $n_{badgers}$ = 2,407, $n_{observations}$ = 4,723), yearlings (age = 1; $n_{badgers}$ = 1,521, $n_{observations}$ = 3,620) and adults (age ≥ 2; $n_{badgers}$ = 1,483, $n_{observations}$ = 6,503). This allowed us to avoid assuming homogeneity of variance components across age categories (though the assumption of homogeneity with increasing adult age remains). We fitted an animal model to each data subset, including fixed effects of *sex*, *season* (spring = March–May, summer = June–August, autumn = September–November, winter = December–February) and for adults-only we included a cubic function of *age*. Random effects included the *additive genetic merit*, a *permanent environment* effect (to account for non-genetic sources of repeatable differences), *maternal identity*, *year* (of observation), *group* (defined by spatial location of home sett) and a factor defined by the *group-by-year* interaction. The latter serves here as a proxy for social environment as it defines the set of individuals interacting most closely in time and space (i.e. within a year of observation at a spatial location). Random effects are assumed to be normally distributed with means of zero and variances (V_A, V_{PE}, V_M, V_{Gr}, V_Y and V_{GrxY}, respectively) to be estimated. For each stage-specific model, we calculated phenotypic variance as the sum of the estimated components and used this to calculate intra-class correlations (conditional on fixed effects). We also tested the significance of V_A, V_M, V_{Gr}, V_Y and V_{GrxY} by LRT. Note we do not test V_{PE} separately or provide an overall test for among-individual variance ($V_A + V_{PE}$) as its presence is inevitable given the progressive definition of $bTB_{capture}$.

Our second strategy for dealing with age specificity was to analyse the full $bTB_{capture}$ data set using a random regression animal model. Specifically, we included random slopes on age (as well as random intercepts) for the additive and permanent environment effects that combine to determine among-individual variance. Other fixed and random effects were specified as described above for the models applied to data subsets. Though this method is widely used to characterize (genetic) variation in reaction norm slopes (interpretable as ageing or plasticity, depending on the x-axis), here the rationale is to fit a model that can accommodate the expected compounding of among-individual variance with age. The random regression model yields estimates of genetic variances in random intercepts and slopes (and the slope–intercept genetic correlation) that can be projected to obtain a 'character state' estimate of the genetic variance-covariance matrix (**G**) among age-specific $bTB_{capture}$ traits (see, e.g., Roff & Wilson, 2014 for equations and a didactic treatment of this strategy). Permanent environment effects are then treated analogously. In practice, we first fitted the model using slopes on a rescaled version of age; we subtracted 2 so that 'zero' on the new scale corresponds to 2-year-old badgers (the modal age class of adults). With this scaling of age, additive genetic and permanent environment intercept variances represent V_A and V_{PE}, respectively, in 2-year-olds (the model class of adults). We then projected the estimated covariance functions to derive corresponding estimates of V_A and V_{PE} at actual ages 0 (cubs), 1 (yearlings) and 4 (the approximate mean age of adult observations in the data) which were used to derive age-specific ICC estimates. Note that while the model assumes that the variance components, except V_A and V_{PE}, are homogeneous, all ICCs are expected to show age-sensitivity (as changes in V_A and/or V_{PE} will alter V_P).

3 | RESULTS

3.1 | Analysis of $bTB_{lifetime}$

Diagnostics on initial MCMCglmm runs suggested poor chain mixing and high levels of autocorrelation across consecutive saved samples of many model parameters. Although this was not readily resolved by adjusting run parameters, the estimated variance components were highly consistent across three runs, all based on a chain length of 3,000,000 with a burn in of 10,000 and thinning interval of 100 (resulting in 29,900 samples in the posterior). We present results based on a single one of these chains. Diagnostic plots and tests for this model fit are presented in Appendix S1. Autocorrelation levels between saved samples remained high, but the use of such long chain allowed us to obtain reasonably large effective sample sizes (>1,500 across all variance components; Appendix S1) and tests for stationarity were passed for all fixed effects and variance components. Posterior distributions (on the latent probit scale) were clearly distinct from zero for V_{NGr}, V_{BY} and V_{NGrxBY} but not for additive and

maternal variance components (Appendix S1). For $V_{A,}$ the posterior shows a local peak that is distinct from zero but also has high density close to zero. For $V_{M,}$ there is no non-zero peak in the posterior distribution visible.

Posterior means of variance components on the probit scale used to generate point estimates ICC on the observed scale (Table 1) indicated that additive genetic effects (h^2 = 0.092) and birth year (ICC = 0.110) and natal group x birth year effects (ICC = 0.087) explain similar amounts of variance in $bTB_{lifetime,}$ while maternal effects were (effectively) absent (posterior mean ICC of < 1%). Fixed effect estimates from this model are not directly relevant to hypotheses being tested but for completeness are shown in Appendix S2 (together with estimated variance components on the probit scale).

TABLE 1 Intra-class correlations (ICC) for the binary measure of lifetime risk of *Mycobacterium bovis* infection ($bTB_{lifetime}$). Estimates presented relate to the observed data scale but are obtained from a generalized model using a probit link. Posterior means are used as point estimates of ICC and 95% credible intervals are also shown

Variance component	ICC	95% CI
additive genetic	0.092	<0.001–0.195
maternal	0.009	<0.001–0.033
birth year	0.110	0.060–0.169
natal group	0.040	0.013–0.073
natal group x birth year	0.087	0.051–0.125

3.2 | Repeated measures models of age-specific $bTB_{capture}$

Analysis of $bTB_{capture}$ provided evidence for changes in the relative importance of genetic and environmental influences on phenotype with age. Analyses of age-specific data subsets provided statistical support for the presence of maternal, year, group and year x group effects in cubs, yearlings and adults (all LRT yielding $p < 0.05$; Table 2). In contrast, statistically significant additive genetic variance was only found in the adult (2 + years) data subset. Estimated heritability (SE) was low in cubs ($h^2 < 0.001$ [0.053]) and undetectable in yearlings (with V_A bound to zero in the model fit), but somewhat higher and statistically significant in adults ($h^2 = 0.119$ [0.062], $\chi^2_{0,1} = 3.75$, $p = 0.026$). Group effects are low with the highest ICC being just 2.4% (in cubs) suggesting little (fixed) spatial heterogeneity in bTB risk. However, ICC for year and group x year effects were somewhat higher (Table 2). Notably in cubs and yearlings, these two components together explain approximately 20% of observed variance in $bTB_{capture.}$ Thus, there is temporal (among-year) variation, some of which is general to the study area, and some of which is

TABLE 2 Likelihood ratio tests of random effect in animal models of $bTB_{capture}$ fitted to age-specific data subsets, and random regression animal model fitted to all data

Age class	Component	χ^2	*df*	*p*
O (cubs)	additive genetic	0.10	0,1	0.377
	maternal	5.05	0,1	0.012
	year	50.4	0,1	<0.001
	group	19.7	0,1	<0.001
	group x year	86.6	0,1	<0.001
1 (yearling)	additive genetic[a]	0.00	0,1	0.500
	maternal	6.46	0,1	0.006
	year	79.6	0,1	<0.001
	group	10.1	0,1	0.001
	group x year	75.7	0,1	<0.001
2+ (adult)	additive genetic	3.75	0,1	0.026
	maternal	8.31	0,1	0.002
	year	36.1	0,1	<0.001
	group	9.36	0,1	0.001
	group x year	234	0,1	<0.001
All (random regression)	additive genetic[b]	7.59	3	0.055
	maternal	53.4	0,1	<0.001
	year	143	0,1	<0.001
	group	21.7	0,1	<0.001
	group x year	288	0,1	<0.001

[a]Additive variance was bound to zero leading to identical log-likelihoods of full and reduced models.

[b]Reduced model contains three fewer parameters, although since negative genetic variances in intercept and slope are precluded use of 3 *df* is conservative for statistical inference.

specific to particular groups. The estimates of the variance components used to calculate ICC are presented in Appendix S3. As in the analysis of $bTB_{lifetime,}$ we note that fixed effects are being used to control for 'nuisance' sources of variance here rather to address any specific hypotheses. Nevertheless, for completeness, fixed effects estimates and the corresponding statistical inference are shown in Appendix S4 for all REML models.

As expected, when modelling all ages simultaneously, the inclusion of random slopes on age for additive and permanent environment effect greatly improved the model (LRT comparison to the equivalent random intercept only model; $\chi^2_4 = 4{,}491$, $p < 0.001$). The random regression model indicated significant contributions of V_M, V_{Gr}, V_Y and V_{GrxY} to variance in $bTB_{capture}$ (Table 2), while support for genetic variance was slightly equivocal. This is because while the presence of genetic variance (modelled as a first order covariance function of age) was marginally non-significant (LRT $\chi^2_3 = 7.59$, $p = 0.055$), we also expect that use of 3 DF in the likelihood ratio test will be rather conservative here (since boundary constraints strictly apply to both slope and intercept variances for which negative values are precluded). Furthermore, the REML estimate of the slope–intercept genetic correlation was fixed to + 1 to keep the genetic covariance structure within allowable parameter space (i.e. variances ≥ 0, −1 ≤ correlation ≤ +1). The perfect slope–intercept correlation means that projected to a character state view, estimated genetic correlations between age-specific $bTB_{capture}$ traits are strongly positive (and effectively + 1 among all ages > 1) while there is a strong pattern of increasing V_A with age (Appendix S3). For permanent environment effects, the equivalent projection reveals a pattern of increase from cubs onwards (as expected given inevitable accumulation of among-individual variance). Estimates of r_{PE} are strongly positive (effectively + 1) between observation ages 1, 2 and 4, but are less between these ages and $bTB_{capture}$ at age 0 (with a minimum of $r_{PE} = 0.38$ between 0 and 4; Appendix S3).

Scaling the variance components estimated with the random regression models to ICC reveals broadly similar patterns to those obtained by age-specific analysis (Figure 2). Specifically, both approaches to modelling $bTB_{capture}$ indicate that heritability is very low in early life while social environment effects (maternal and group x year) are important in the youngest badgers. Conversely, heritable variation is present in adults. Under the random regression model, estimated heritability (SE) goes from zero in cubs, to 0.134 (0.580) at the modal adult age of 2 years and increases to 0.206 (0.078) at 4 years. Some differences between the results of the two modelling strategies are also apparent. Most notably the age-specific subset

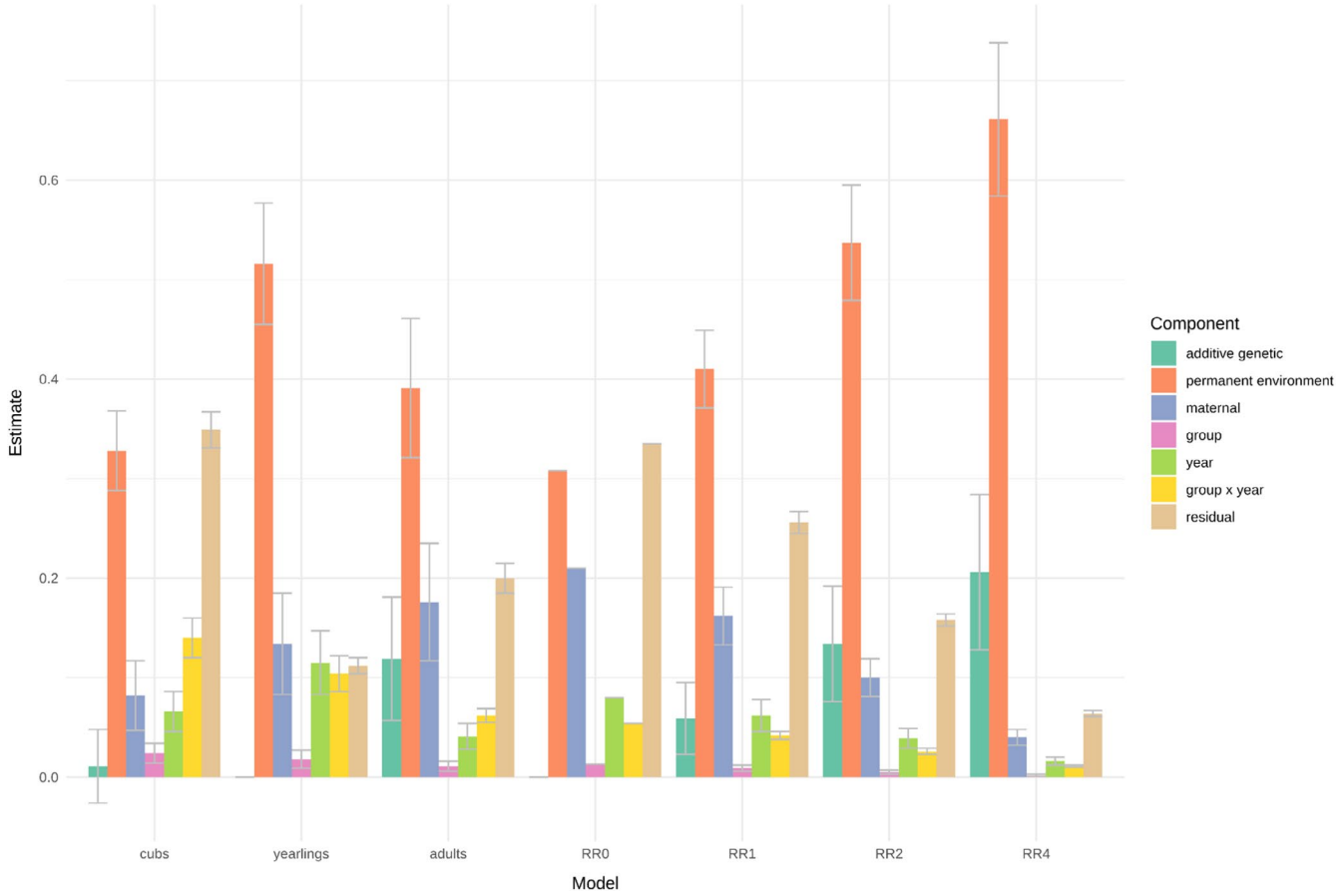

FIGURE 2 Estimated heritabilities and intra-class correlations for $bTB_{capture}$. Estimates from analyses of age class-specific data subsets (cubs, yearlings, adults) are shown, together with estimates from the random regression (RR) model evaluated at ages 0, 1, 2 and 4 years. Error bars indicate ± 1*SE* but could not be obtained for ICC at age 0 under the random regression model (see Appendix S3 for explanation of this)

analysis actually indicates increasing relative importance of maternal effects with age, while m^2 (the ICC corresponding to maternal variance) declines under the random regression model (from $m^2 = 0.21$ at age 0 [cubs] to 0.04 at age 4). However, interpretation is slightly nuanced here, as maternal influences at early ages will tend to contribute to fixed among-individual differences (and so be partitioned as V_{PE}) at later ages under the random regression formulation. This will not happen to the same extent in models of yearling and adult data subsets. The same effect may also explain the slightly lower estimates of the group x year ICC under the random regression model.

4 | DISCUSSION

Here, we examined *M. bovis* infection status in a naturally infected population of European badgers, to ask whether, and to what extent, genetic and environmental (including social and maternal) effects contribute to variation among individuals in disease risk and progression. Using two measures of infection status ($bTB_{capture}$, a progressive measure of disease at each capture event and $bTB_{lifetime}$, a binary lifetime infection score), animal model analyses support the presence of a relatively small, but non-zero, heritable component of infection status. Analyses of $bTB_{capture}$ show that heritability is very low in cubs and yearlings but higher in adults. Temporal (among-year) variation is present in the population as a whole, as expected, while group identity effects (interpretable as temporally fixed spatial heterogeneity) are detectable, but do not explain much variance in either $bTB_{lifetime}$ or $bTB_{capture}$. In contrast, group x year effects are important in all analyses and are most parsimoniously interpreted as social effects, reflecting shared infection risk of animals closely associating in space and time. The importance of maternal identity effects—both in relative and absolute terms—is less clearly resolved by our analyses (discussed further below).

4.1 | Genetic variation in bTB status and progression

Variation in the lifetime risk of infection and in progression of bTB (as measured by $bTB_{capture}$ across repeated measures) both has a partial genetic basis. The heritability of the former is estimated at 0.092, while our models suggest h^2 for $bTB_{capture}$ is very low among young animals but increases with observation age (e.g., to 0.134 in two-year-old adults, based on the random regression model). Most variation in bTB infection status therefore arises from environmental effects (broadly defined) rather than genetic factors. This is not surprising and mirrors findings in cattle where estimates of h^2 for bTB resistance range from 0.06 to 0.18 (Allen et al., 2010). Interestingly, using an experimental infection approach, h^2 of bTB resistance to *M. bovis* was estimated at 0.48 in a population of farmed red deer (*Cervus elaphus*; Mackintosh et al., 2000), a species that, in some ecological contexts, is also thought to act as an important wildlife reservoir for this disease (Delahay et al., 2007; Vicente et al., 2006). This much higher estimate was obtained from parent–offspring regression (a method which can be more prone to upward bias from common environment effects), but could also reflect the experimental infection design used. Specifically, we stress that neither $bTB_{lifetime}$ nor $bTB_{capture}$ provides a measure of resistance alone. Rather these phenotypes will be outcomes of multiple contributing traits and processes (e.g. behavioural exposure risk, resistance, tolerance) that may themselves differ in their extent of genetic control.

Since there are few heritability estimates for disease traits in wild vertebrate populations, a consensus on the importance of standing genetic variation is yet to emerge. A number of studies have found additive genetic variation for host defence traits, including resistance to strongyle nematodes in feral sheep ($h^2 = 0.13$ *SE* 0.04) inferred from nematode-specific antibody titres; Hayward, Garnier, et al., 2014) and both resistance (inclusive heritability 0.176 CI 0.072–0.322) and tolerance to copepod parasites in a freshwater cyprinid fish (Mazé-Guilmo et al., 2014). Conversely, experimental studies failed to detect any influence of host genotype on cell-mediated immune responses in house martins *Delichon urbica* (Christe et al., 2000) and house wrens *Troglodytes aedon* (Sakaluk et al., 2014). Interestingly, across three populations of tree swallow *Tachycineta bicolor*, Ardia and Rice (2006) found no heritable variation for immune function in two populations, while an estimate of $h^2 = 0.42$ was reported for the third.

While it seems quite possible that generalizations about the contribution of genetic factors to variation in disease outcomes will be difficult (even among populations of the same species), our analyses of $bTB_{capture}$ do highlight the importance of considering age specificity. At least initially, an increase in phenotypic variance with age is an inevitable consequence of trait definition and measurement here; the pattern of increasing h^2 with age thus arises because V_A goes up proportionately faster than the total phenotypic variance V_P. Importantly, age specificity of heritability does not however imply that underlying risk factors themselves (whether genetic or otherwise) must have age-specific action. This is because small (but age-invariant) differences in infection risk will generate more and more variance in infection status as time available to acquire infection increases. So, while age (or stage-)-specific gene action could contribute to the pattern of increasing h^2, it is not required to explain the pattern. Regardless, the main implication of low trait heritability in cubs and yearlings is that any early-life natural selection acting through juvenile viability has very limited scope to affect an evolutionary response. Conversely, a response is predicted if selection against bTB infection acts through adult fitness components. Though we do not have formal estimates of selection, two recent studies have both failed to detect costs of infection on reproductive success in this badger population (McDonald et al., 2016; Tomlinson, Chambers, Carter, et al., 2013; Tomlinson, Chambers, Wilson, et al., 2013). However, adult badgers (particularly males) with advanced infection states do show increased mortality rates (Graham et al., 2013; McDonald et al., 2016).

An important caveat in interpreting our heritability estimates is that the serological tests and bacterial culture used to define phenotypes have relatively low levels of sensitivity. This means that an unknown, but certainly non-zero, proportion of truly infected animals will not have been correctly phenotyped. For example, intermittent excretion and latent infection characteristic of *M. bovis* infection (Clifton-Hadley et al., 1993; Gallagher et al., 1998) limit the sensitivity of bacterial culture whilst antibody tests may fail to detect infection either due to the absence or low concentrations of antibody produced or inclusion of an inappropriate antigenic target. Assuming that propensity to test negative when truly infected is not itself a heritable trait, this form of measurement error should be partitioned into generic residual and (for $bTB_{capture}$) permanent environment variances and so may contribute to relatively low heritabilities (as well reducing ICC for all non-generic environmental effects). If so, improved confidence in assigning individual infection status (e.g., use of probabilistic approaches to incorporate full test histories, Buzdugan et al., 2016) may be needed to gain greater resolution on genetic factors predisposing to disease.

4.2 | Social effects tend explain more variation than genetic factors

In total, social environment effects, estimated as the sum of group x year and maternal variances appeared to explain more variation in $bTB_{capture}$ than genetic factors. This is certainly the case for cubs and yearlings and was also true for the estimates derived from analysis of the adult data only. Under the random regression model, genetic and social effects account for similar proportions of variance at age 2 years, while genetic effects are predicted to dominate at 4 years. However, as noted earlier, under this modelling approach where only V_A and V_{PE} were allowed to vary with age we expect 'permanent' non-genetic effects from early life (that may include, for instance maternal influences) to accumulate in V_{PE} with age, somewhat complicating interpretation. In principle, it is possible to allow age-dependence of all random effects within the random regression model, but initial exploration of models with additional random slopes led to instability, convergence problems and implausible levels of predicted phenotypic variance in adults.

Spatial clustering of infection at the social group level has been reported previously in badger populations, with some groups in the Woodchester Park population remaining test negative for long periods (Delahay et al., 2000; Vicente et al., 2007). As (natal) group identity coincides with main sett location in the study area, whether this observation can be explained by spatial heterogeneity in the habitat rather than social effects per se has remained unclear. However, our finding that most group effects were year-specific (i.e., partitioned as group-by-year variance) strongly suggests a social origin (since group composition varies on a year-to-year basis whereas location is fixed in time). It also corroborates previous studies that suggest the importance of social processes (but which did not control for potentially confounding genetic or maternal effects). For instance, social network analyses have revealed evidence suggesting a positive association between bTB infection and levels of extra-group contact (Silk et al., 2018; Weber et al., 2013). Extra-group contacts may include temporary excursions for breeding purposes, the rates of which have recently been found to vary among social groups (Marjamäki et al., 2019). Seasonal variation in bTB incidence (accounted for in our models by the fixed effect structure) has also been shown to correlate with peaks of within-group social contact (Silk, Weber, Steward, Delahay, et al., 2017), although indirect transmission (e.g. via environmental contamination of communal latrines and setts) may also occur (Courtenay et al., 2006; Drewe et al., 2010).

The contribution of maternal (identity) effects to bTB risk and progression in Woodchester Park badgers is not fully resolved by our study. In particular, the Bayesian analysis of $bTB_{lifetime}$ provided no evidence of among-mother variance in offspring lifetime risk, while maternal identity was a statistically significant predictor of $bTB_{capture}$ in all REML models fitted. Based on the results in their entirety, we cautiously conclude that maternal effects exert at least some influence on bTB status among badgers in the present study. Assuming so, this adds further support to the view that early-life environments impact bTB infection risk (Tomlinson, Chambers, Carter, et al., 2013; Tomlinson, Chambers, Wilson, et al., 2013). It also suggests the reported positive association between cub infection and presence of infected relatives (Benton et al., 2016; Delahay et al., 2000) could be driven by a combination of both maternal and additive genetic effects. Though widely observed for life-history, reproductive and growth traits, maternal effects on disease risk have been less well documented in other wild vertebrates (but see, e.g., Hall & Ebert, 2012; Seppälä & Langeloh, 2016). However, in Soay sheep maternal effects on offspring parasite load appear, at least in part, to occur through maternal age and parasite load (Hayward et al., 2010). However, in that population and in some domestic sheep quantitative genetic analyses also support a contribution of maternal effects to nematode resistance (Coltman et al., 2001; Stear et al., 2001) and to helminth-specific immune responses in lambs (Sparks et al., 2019). Our data are not informative for specific mechanisms, although similarity among maternal siblings (over and above that attributable to additive genetic and social group effects) could arise from maternal provisioning of antibodies, variation in maternal infection status or differential contact time with cubs. Second order mechanisms are also possible, for instance if maternally influenced nutritional status has consequences for cub immune responses.

Whether or not the magnitude of maternal effect contributions to variation in bTB status declines with age in Woodchester Park badgers is unclear. On the one hand, maternal effects on $bTB_{lifetime}$ were absent and random regression model for $bTB_{capture}$ yielded only a small maternal ICC estimate (5%) in adults by age 4. On the other, this second result may be a consequence of model specification (with early acting maternal effects having permanent effects that are partitioned to V_{PE} rather than V_M in late life) while the highest maternal ICC estimated was for $bTB_{capture}$ in the adults-only data subset (18%). We suspect this lack of consistency arises from a data structure that is far from ideal for partitioning additive genetic from maternal (and

common environment) effects. In particular, the pedigree is very incomplete and while some females contribute multiple offspring (to a maximum of 11), the mean number of offspring among the 537 known mothers is just 1.07. For this reason, we also elected not to attempt further decomposition of the estimated maternal variances into maternal genetic and environmental components (e.g., following McAdam et al., 2014; Wilson, Coltman, et al., 2005).

4.3 | Caveats arising from the consideration of genotype(social)–environment correlation

As noted earlier, the preponderance of within-group paternities in the Woodchester Park population (63% within-group v .37% extra-group paternity, Marjamäki et al., 2019) means that genetic relatedness is, on average, greater for pairs of individuals that share a (natal) social group environment than for pairs that do not. Similarly, siblings necessarily share a maternal environment. The population is thus characterized by a 'genotype–environment correlation' that cannot easily be disentangled. Since experimental approaches (e.g. cross-fostering; Kruuk & Hadfield, 2007) are not appropriate in this or similar systems, we have taken the conservative approach (with respect to estimation of h^2) of simultaneously modelling additive genetic, maternal and social group (including group x year) effects. Failure to model common environment effects, including mothers and shared habitat use by relatives is a well-known potential source of upward bias in h^2 estimates (e.g., Regan et al., 2015; Stopher et al., 2012; Wilson, Coltman, et al., 2005). However, accurate separation of correlated genetic and environmental effects necessarily depends on data structure and quality. Here, incomplete parentage data are likely to have produced errors in the pedigree (e.g., unrecognized relatedness among true siblings) even in the unlikely event that all parentage assignments made are correct. Although pedigree error will usually downwardly bias the estimation of h^2 (Morrissey et al., 2007), the consequences are not so readily predicted here, given the kin-biased social group structure, and the fact that maternal and paternal identities are both similarly uncertain.

5 | CONCLUSIONS

The long-term study of the Woodchester Park badger population provides a unique and valuable opportunity to investigate the factors driving among-individual variation in *M. bovis* infection status. We have found that genetic factors play a small but significant role in structuring variation in infection status, particularly in older (adult) badgers. However, it is clear that social influences arising from interactions among animals clustered in space (group) and time (year) and from maternal effects are also important. Genetic and social effects may influence observed bTB infection status through multiple pathways, including via infection risk (e.g., through behavioural traits), resistance, and/or ability to limit damage caused (tolerance). Though not mutually exclusive, resistance and tolerance in particular are predicted to have very different consequences for parasite fitness; by limiting parasite growth, resistance will negatively impact parasite fitness, while tolerance can, in fact, promote parasite fitness by increasing the period over which transmission might occur. Given the implications of individual variation in infectiousness for the long-term persistence of parasites (Kramer-Schadt et al., 2009) and micro-evolutionary dynamics of both host and parasite (Best et al., 2008), determining whether genetic and environmental determinants of *M. bovis* infection status and the severity and progression of bTB operate through resistance, tolerance, or both should be a useful—if empirically challenging—priority.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

A.J.W., R.A.M., R.D. and P.H.M. designed research; P.H.M performed research; R.D. contributed data; P.H.M. analysed data with A.J.W. and H.L.D; P.H.M. led the write-up with input from all authors.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data used in this study are publicly archived in Open Research Exeter (ORE) at https://doi.org/10.24378/exe.3104

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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